REMARKS

Claims 2, 4, 6, 9, 14-19 and 21-24 are pending. No amendments have been made by way of the present submission, thus, no new matter has been added.

In view of the following remarks Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Interview held on February 16, 2005

Applicants take this opportunity to sincerely thank the Examiner, as well as the Supervisory Patent Examiner for the interview conducted on February 16, 2005. Based upon the discussion during this interview, Applicants have prepared the following arguments, as well as a Declaration pursuant to 37 C.F.R. § 1.132.

Issues Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 2, 4, 6, 16, 17, 18, 22, and 23 under 35 U.S.C. § 103(a) as being obvious over Gorski et al. (*Clinical Chemistry*, 43(1):193-195, 1997) in view of Maatman et al. (*Biochem. J.* 288:285-290, 1992) and Simon et al. (*J. Biol. Chem.* 272(16):10652-10663, 1997).

The Examiner has rejected claim 9 under 35 U.S.C. § 103(a) as being obvious over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Kimura et al. (*J. Biol. Chem.*, 266(9):5963-5972, 1991).

The Examiner has also rejected claims 19 and 21 under 35 U.S.C. § 103(a) as being obvious over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Galaske et al. (*Pflugers Archives Euro. J. Physiol.*, 375(3):269-277, 1978).

Lastly, the Examiner has rejected claims 14 and 15 under 35 U.S.C. § 103(a) as being obvious over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Zuk et al. (United States Patent No. 4,281,061).

In view of the following remarks, as well as the Declaration pursuant to 37 C.F.R. §1.132 attached hereto, Applicants respectfully traverse the above rejections and request that the Examiner withdraw all rejections and allow the currently pending claims.

Inquiry Concerning Claim 24

As a preliminary matter, Applicants draw the Examiner's attention to fact that although the Office Action Summary (page 1 of the January 12, 2005 U.S.P.T.O. Communication) indicates that claim 24 is both pending and rejected, none of the current rejections includes claim 24. Accordingly, Applicants respectfully request that the Examiner provide action on the merits with respect to claim 24.

The Present Invention and Its Advantages

The main independent claim currently pending is claim 16. Claim 16 relates to a method for diagnosis or prognosis of a kidney disease in human, which comprises the steps of:

(a) preparing a specimen collected from a human;

(b) detecting liver-type fatty acid binding protein contained in said specimen; and

(c) diagnosing or prognosing the kidney disease based on the test result of the detection in (b).

Prior to the present invention, there existed no method for diagnosis or examination of a patient utilizing a relationship between liver-type fatty acid binding protein (L-FABP) in kidney tissues and the prognosis of kidney diseases. That is, the present inventors have been the first to discover a relation between L-FABP and the prognosis of kidney diseases. Thus, the present invention relates to a method for examining kidney disease, which involves detection of L-FABP contained in the specimen. The present invention thus provides for the prognosis and diagnosis of various kidney diseases, for instance, diabetic nephropathy, glomerulonephritis, nephritic syndrome, focal glomerulosclerosis, immune complex nephropathy (IgA nephropathy, membranous nephropathy, etc.), lupus nephritis, drug-induced renal injury, renal insufficiency and kidney graft rejection.

Each of the Examiner's rejections relies upon the combined references of Gorski, Maatman and Simon. However, Applicants respectfully submit that these references, whether taken individually or in combination, fail to suggest or disclose the presently claimed subject matter. In particular, there is no motivation upon which one of ordinary skill in the art would rely in order to construct the present invention.

Brief Summary of Arguments

Gorski discloses a study which details the concentrations of heart-tpe (H-) FABP with respect to chronic renal failure. The Examiner's argument is that one of ordinary skill in the art would utilize the teaching of Maatman, relating to liver-type fatty acid binding proteins, to modify the reference of Gorski. However, Applicants respectfully submit that there exists no motivation to replace the H-FABP of Gorski with the L-FABP of Maatman. That is, there is no indication that H-FABP and L-FABP are "functional equivalents".

The secondary reference of Maatman simply discloses that the content of H-FABP and L-FABP mRNAs in the kidney is similar. However, similar transcription levels do not necessarily correlate with similar function, especially since the amino acid homology between H-FABP an L-FABP is low. Thus, one of ordinary skill in the art would not consider H-FABP and L-FABP to be interchangeable. Further, Applicants respectfully submit that Maatman only provides mere speculation as to the function of L-FABP, and this speculation cannot provide adequate motivation for one of ordinary skill in the art to replace the H-FABP of Gorski with the L-FABP of Maatman.

Distinctions Between the Present Invention and the Cited Art

In order to further discuss the deficiencies of the Examiner's rejections, Applicants will first summarize the main references of Gorski, Maatman and Simon. The Examiner relies on each of those references in each rejection. Please note that

although Applicants are addressing these references individually, it is submitted that even the combined disclosure of these references cannot render the present claims *prima facie* obvious.

Gorski et al.

Gorski et al. discloses that "Plasma FABP concentration is markedly increased in patients with chronic renal failure." The study of Gorski was done by focusing attention on FABP as a marker for myocardial infarction, and thus the FABP of Gorski is "heart-type FABP (H-FABP)". Gorski are completely silent concerning "liver-type FABP (L-FABP)". Thus, Gorski fails to suggest or disclose the concept of diagnosis of kidney disease by using FABP much less L-FABP.

Maatman et al.

Maatman discloses the existence of L-FABP and H-FABP in human kidneys, and further include speculation that L-FABP may inhibit nephrotoxicity by binding with drugs. However, the "possibility" of inhibition of nephrotoxicity with L-FABP is not related to the diagnosis of a kidney disease with L-FABP. Thus, Maatman fails to suggest or disclose the diagnosis of kidney disease in a human.

Further, Applicants submit that the H-FABP and L-FABP of Maatman are not considered to be similar to, or equivalent to each other.

Simon et al.

The Simon reference is concerned with control of the expression of L-FABP. Further, Simon disclose that a DNA sequence ("heptad repeat") existing in an upsteam region of the L-FABP gene has a function of inhibiting expression of L-FABP in mouse kidney. However, Simon also fails to suggest or disclose the diagnosis of kidney disease in a human.

Briefly, none of Gorski, Maatman, or Simon suggest or disclose the diagnosis of kidney disease in a human using L-FABP. This represents a major deficiency. Futher, Applicants submit that there exist numerous problems in combining Gorski with Maatman and/or Simon, and in replacing the H-FABP of Gorski with L-FABP to reach to the present invention. These problems, which result in a lack of motivation are discussed below:

(i) H-FABP and L-FABP are not similar to or equivalent to each other:

The Examiner apparently considers that H-FABP and L-FABP are similar and/or functional equivalent (do not markedly differ). Thus, the Examiner appears to believe that it is easy to replace H-FABP with L-FABP. That is, the Examiner points out in the outstanding Office Action, page 9, 1st paragraph, lines 5-10 as follows:

"Maatman et al. discloses that "Based on the RT-PCR and hybridization results, the content of the mRNAs of the liver and heart FABP types do not differ markedly in kidneys of male and female rats." See page 289, 1st column and Figure 6. Therefore,

one of ordinary skill in the art at the time of applicant's invention would have been motivated to replace the H-FABP of Gorski et al. with the L-FABP taught by Maatman et al. and Simon et al. because the two types of FABP (heart and liver) were functional equivalents (do not differ markedly)".

Similar comments are also found in other passages in the outstanding Office Action, such as page 10, lines 5-7 (2nd paragraph); page 11, lines 7-9 (2nd paragraph); page 11, line 4-6 (3rd paragraph); page 12, lines 7-9 (1st paragraph); and page 13, lines 6-7 (2nd paragraph).

However, H-FABP and L-FABP are neither similar nor equivalent (nor functionally equivalent) whether viewed from the standpoint of Maatman or from the standpoint of Gorski. This is explained below:

(a) The view from Maatman

Firstly, Maatman disclose the existence of both of H-FABP and L-FABP in the kidney but they also clearly mention the difference of H-FABP and L-FABP. That is, it is clearly mentioned that H-FABP and L-FABP are different in ligand specificities and cellular distributions. The difference in ligand specificities will be understood from the following description:

"The significance of the occurrence in kidney of two FABP types with different ligand specificities and cellular distributions requires further investigation" (cf. page 289, right column, 2nd paragraph, lines 10-12 of Maatman).

"The liver-type FABP also binds some drugs [2,3], and may in this way prevent nephrotoxicity. The heart-type FABP only binds fatty acids and seems to be involved in lipid metabolism." (cf. page 289, right column, 1st paragraph, lines 8-10 of Maatman).

Besides, there is the difference in cellular distributions, that is, "H-FABP exists in the heart and the kidney but does not exist in the liver but on the other hand L-FABP exists in the liver and the kidney but does not exist in the heart", and further "(contrary to H-FABP) L-FABP exists topically in proximal tubules in human", which will be understood from the following description.

"The rat heart FABP cDNA could be demonstrated on the blot, to be present in rat heart and kidney mRNA but not in rat liver mRNA (Fig. 6). The blot ... showed the presence of liver FABP mRNA in both liver and kidney mRNA, but not in heart mRNA (Fig. 6)" (page 289, left column, 2nd paragraph, lines 1-6, and Fig. 6 of Mautman).

"The cellular distribution of the heart-type FABP is similar in rat kidney to the previously found in human kidney [7]. The liver-type FABP, however, is restricted to the proximal convoluted and straight tubules in human kidney [7]" (page 288, right column, 1st paragraph, lines 7-11).

Further, the passage pointed out by the Examiner (page 289, left column, 2nd paragraph, lines 8-10 and Fig. 6) discloses the following:

"Based on the RT-PCR and hybridization results, the content of the mRNAs of the liver and heart FABP types do not differ markedly in kidneys of male and female rats."

However, as the results of detection at the protein level (ELISA test) reveal that there was difference in the ratio of H-FABP and L-FABP as follows:

"ELISA showed low amounts of liver-type FABP in rat kidney cytosol (Table 2). The concentrations are much lower than those of the heart-type FABP, and the ratio of liver and heart-type FABPs differs considerably from that in man." (d. page 288, left column, 2nd paragraph, lines 1-4 and Table 2 of Maatman).

As is clear from the above explanation, according to the description of Maatman, H-FABP is neither similar nor equivalent to L-FABP, but rather, it is clearly described that both are different types of FABP. The Examiner must view the reference as a whole and cannot simply conclude that L-FABP and H-FABP are similar/equivalent by picking and choosing selected passages favorable to his interpretation. This amounts to hindsight reconstruction.

(b) The view from Gorski

In Gorski the FABP (H-FABP) is understood to be heart-derived FABP as is clear from the following description:

"Heart and skeletal muscles contain the same type of FABP [referred to as heart-type (H)-FABP][1,2]...FABP is released from the heart early after the onset of

infarction, whereafter its plasma concentration increases manyfold [3-6]" (page 193, right column, lines 8 -19 of Gorski).

Thus, Gorski confirms that H-FABP exists in the heart. Gorski is completely silent concerning the existence of L-FABP in the heart.

The above has been well known in this field, as mentioned also in Van Nieuwenhoven et al." Lipids, vol. 31, Suppl., pp. S223-S227, 1996, Table 2 etc. (which was submitted as IDS dated Oct. 3, 2002) and Veerkamp et al., Prog. Lipid Res., Vol. 34, No.1, pp.17 -52, 1995, Table 3, etc. (which was filed as Exhibit 3 with REPLY UNDER 37 C.F.R. § 1.111 dated July 22, 2003). Van Nieuvenhoven et al. reference corresponds to reference [1] in Gorski.

Similar description is also found in Maatman, page 289, left column, 2nd paragraph, lines 1-6 as mentioned above.

Thus, a person skilled in the art understands that H-FABP exists in the heart but on the other hand, L-FABP does not exist in the heart. Thus, the H-FABP disclosed in Gorski (existing in the heart) is clearly distinguished from L-FABP (not existing in the heart). Thus, further evidence exist that the two FABPs are neither similar nor equivalent.

Accordingly, from the viewpoint of both Maatman and Gorski, H-FABP and L-FABP are neither similar nor equivalent. Thus, the two FABPs are lacking in similarity/equivalence such that H-FABP would not be replaced by L-FABP.

(ii) Speculation mentioned in Maatman

It described in Maatman as follows:

"We can only *speculate* on the physiological relevance of the two FABP types in kidney. The liver-type FABP binds various ligands and may be involved in the renal excretion of exogeneous and endogeneous metabolites. The liver-type FABP also binds some drugs [2.cl.] and may in this way prevent nephrotoxicity (emphasis added)" (cf. page 289, right column, lines 4-10 of Maatman).

As is mentioned by the authors themselves as "We can only speculate", this description is mere speculation. Further, the speculation is only as to physiological relevance/function of FABP, but never suggests or discloses the diagnosis of kidney disease.

The Examiner points out the description of "The liver-type FABP also binds some drugs, and may in this way prevent nephrotoxicity."

First, it should be noted, "nephrotoxicity"* is the property owned by the drug itself but not the "kidney disease" per se. Note *: According to a dictionary, "nephrotoxicity" means the quality of being toxic or destructive to kidney cells. (cf. the attached copy of Doriand's Illustrated Medical Dictionary 27th edition, p. 1108).

Second, there is no common knowledge that markers for diagnosis of diseases are mostly a substance having an inhibitory activity of the disease. On the other hand, it is usually considered that even though a biological material "X" can inhibit a disease, it

is not said that the material "X" can be used for diagnosis of the disease, in other words, there is no direct relation between the activity for inhibiting a diseases and the diagnosis of the disease.

Accordingly, the speculation of Maatman (that is, speculation of a possibility for inhibition of nephrotoxicity) is unrelated to a suggestion of using L-FABP for diagnosis of kidney disease. The speculation thus cannot constitute motivation for combining Maatman with Gorski nor for replacing H-FABP with L- FABP.

Obviousness must be predicted on something more than it would be obvious "to try" the particular class of solvent recited in the claims or the possibility it will be considered in the future, having been neglected in the past. Ex parte Argabright et al., 161 U.S.P.Q. 703 (POBA 1967). However, this is exactly what the Examiner is contending. In the present instance, evidence exists that H-FABP and L-FABP are not equivalent. Nonetheless, the Examiner asserts that the mere recitation of these two FABPs provides motivation to replace the H-FABP of Gorski with the L-FABP of Maatman.

However, even if H-FABP and L-FABP are equivalent, a point not conceded by Applicants, there still exists no motivation in the cited art to use L-FABP in the diagnosis/prognosis of kidney disease. At best, Maatman provides "speculation" concerning the role of the two FABPs in the kidney. However, "speculation" cannot serve as a basis for obviousness. Mere speculation simply amounts to a "possibility" of

a relation between L-FABP and the kidney, much less a specific relation between L-FABP and diagnosis of kidney disease. Thus, the Examiner's rejection at best amounts to an "obvious to try" rejection. However, "obvious to try" is not a valid test of patentability. Id., see also In re Mercier, 185 U.S.P.Q. 774 (CCPA 1975); Hybridtech Inc. v. Monoclonal Antibodies, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

(iii) Lack of correlation between Gorski and Maatman:

Gorski does not aim at the kidney-type FABP and hence fail to even suggest kidney-type FABP. Also, Maatman does not aim at diagnosis of diseases (neither diagnosis of kidney disease nor diagnosis of heart disease) and hence fail to even suggest anything with respect to diagnosis of diseases.

Thus, both Gorski and Maatman have separate disclosures as to "H-FABP" and "kidney" without any relation to each other. For this additional reason, there is no motivation to combine both literatures.

The above is also applicable to the other cited reference of Simon. That is, Simon discloses control of expression of L-FABP. That is, a DNA sequence (designated as "heptad repeat") inhibits the expression of L-FABP. This may be somewhat relevant to Maatman as far as it is concerned with L-FABP in the kidney. However, it has little relation with the disclosure of Gorski.

(iv) Gorski includes negative disclosure concerning the possibility of the application of H-FABP to diagnosis of kidney disease:

Gorski discloses that "plasma FABP [H-FABP] concentration is markedly increased in patients with renal failure" (page 194, right column, 2nd paragraph, lines 1-6 and Table 1 of Gorski).

On the other hand, Gorski also mentions a detailed analysis of the results shown in Table 1 as follows:

"Neither plasma FABP [H-FABP] nor plasma myoglobin concentrations showed a correlation with the period of dialysis or urea or creatinine concentration in plasma" (page 194, right column, 1st paragraph, lines 10-14 and Table 1 of Gorski).

That is, based on the experimental results that plasma creatinine and urea decreased after dialysis in comparison with those before dialysis, but H-FABP did not show such change in the same tests, Goski states that there was no correlation between FABP (H-FABP) and creatinine or urea.

However, creatinine and urea have widely been used as a marker for diagnosis of kidney disease. Accordingly, the above description of Gorski would be interpreted by one of skill to mean that H-FABP cannot be used like the creatinine or urea which are markers for kidney disease. That is, the description of Gorski represents a negative teaching concerning of the application of H-FABP to the diagnosis of kidney disease.

With such a negative description, those of skill in the art would never expect that H-FABP may be successfully applicable to the diagnosis of kidney disease even

though the skilled person might have understood that plasma FABP increased in kidney failure.

(v) By replacing the H-FABP of Gorski with other molecule, there is no reasonable expectation of obtaining the same results:

As mentioned above, Gorski discloses that "plasma FABP [H-FABP] concentration is markedly increased in patients with renal failure". Gorski also explain that the clearance in kidney is different between H-FABP and myoglobin as follows:

"These findings suggest that the kidneys play a more dominant role in the clearance of plasma FABP [H-FABP] than of myoglobin" (page 194, right column, 2nd paragraph, lines 21-24 of Gorski).

It is noted that FABP [H-FABP] and myoglobin are considered to be markers for heart disease and a low-molecular-mass protein in Gorski as follows:

" ... these proteins have similar molecular masses (15 and 18kDa, respectively) and show a similar plasma release curve in patients with acute myocardial infarction and normal renal function" (page 194, right column, 2nd column, lines 16-21 of Gorski). It is thus mentioned that even such similar molecules are still different in the clearance in kidney.

Accordingly, a person skilled in the art will certainly question whether the same results would be obtained by replacing H-FABP of Gorski with another molecule. In

fact, the skilled person would have assumed that the H-FABP could not be replaced with other molecule with a reasonable expectation of success.

(vi) Distance between the present invention and the cited references:

From the above various explanations, Applicants submit that the present invention is unobvious over the cited references. However, to further reinforce this point Applicants take this opportunity to explain just how far apart the present invention is from the cited art.

In order to reach to the present invention from the cited references, it is required at least the following two steps i) and ii).

i) A change in reasoning must be required so that the focus of Gorski is moved to "diagnosis of kidney disease", and

ii) The H-FABP of Gorski must be replaced with L-FABP of Maatman.

However, it is not easy to achieve the above steps i) and ii) as is explained below.

(a) Difficulty of the change in reasoning to move the focus to "kidney of disease":

Gorski aim at the diagnosis of heart disease (the diagnosis of heart disease by H-FABP). It is disclosed in Gorski that H-FABP increased in kidney diseases, but this description does not directly teach that H-FABP can be used for diagnosis of kidney

disease. Thus, it is required to change the thinking so as to move the focus into "dialysis of kidney disease.

However, as mentioned above, Gorski includes a negative description with respect to the possibility of the application of H-FABP to the diagnosis of kidney disease. It would thus be very difficult to make the change in reasoning to move the focus to the diagnosis of kidney disease by overcoming such a negative teaching.

(b) Difficulty of replacement of H-FABP of Gorski with L-FABP of Maatman:

First, in Gorski H-FABP and L-FABP are not similar and/or equivalent to each other and it is not easy to replace to each other. Further there is no motivation to replace both, as is explained in the above (i) and (ii). Additionally, there is no reason to combine Gorski with Maatman as is explained in the above (iii).

Second, any person skilled in the art would never expect that H-FABP of Gorski will easily be replaced with other molecule successfully as is explained in the above (iv).

Accordingly, Applicants submit that it would be quite unlikely to replace H-FABP of Gorski with the L-FABP of Maatman.

Accordingly, Applicants submit that it will be not easy to overcome both of the above step i) and ii), and unless at least these steps i) and ii) are overcome, the present invention cannot be achieved. Accordingly, the present invention cannot be considered obvious over the combination of Gorski with Maatman and Simon.

Declaration under 37 C.F.R. § 1.132

Further, Applicants have provided a Declaration pursuant to 37 C.F.R. §1.132 which clearly explains that there is no proper motivation to combine references as suggested by the Examiner. In fact, there would be no reasonable expectation of success in such a combination. Accordingly, the Examiner is respectfully requested to withdraw all outstanding rejections and allow the currently pending claims.

Applicants also point out that although the Examiner has rejected other claims, for instance claims 9, 14, 15, 19 and 21 under Gorski, Maatman, Simon and other various secondary references, Applicants respectfully submit that the additional references fail to overcome the deficiencies in the main rejections based upon Gorski, Maatman and Simon. Accordingly, each of these rejections are likewise overcome for the same reasons discussed above.

In summary, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

If the Examiner has any questions or comments, please contact Craig A. McRobbie (Registration No. 42,874) at the office of Birch, Stewart, Kolasch and Birch, LLP.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $120.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: May 12, 2005

Respectfully submitted,

By #42,874

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Attachment: Declaration Under 37 C.F.R. § 1.132 (including exhibits A-D)
Excerpt from Dorlands Illustrated Medical Dictionary

GMM/CAM/cms

Exhibit A

AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

Mark J. Sarnak, MD, Cochair; Andrew S. Levey, MD, Cochair; Anton C. Schoolwerth, MD, Cochair; Josef Coresh, MD, PhD; Bruce Culleton, MD; L. Lee Hamm, MD; Peter A. McCullough, MD, MPH; Bertram L. Kasiske, MD; Ellie Kelepouris, MD; Michael J. Klag, MD, MPH; Patrick Parfrey, MD; Marc Pfeffer, MD, PhD; Leopoldo Raij, MD; David J. Spinosa, MD; Peter W. Wilson, MD

Chronic kidney disease[1] (CKD) is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. The number of individuals with kidney failure treated by dialysis and transplantation exceeded 320 000 in 1998 and is expected to surpass 650 000 by 2010.[1,2] There is an even higher prevalence of earlier stages of CKD (Table 1).[1,3] Kidney failure requiring treatment with dialysis or transplantation is the most visible outcome of CKD. However, cardiovascular disease (CVD) is also frequently associated with CKD, which is important because individuals with CKD are more likely to die of CVD than to develop kidney failure.[4] CVD in CKD is treatable and potentially preventable, and CKD appears to be a risk factor for CVD. In 1998, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD.[5] This report showed that there was a high prevalence of CVD in CKD and that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population (Figure 1 and Table 2).[6–18] The task force recommended that patients with CKD be considered in the "highest risk group" for subsequent CVD events and that treatment recommendations based on CVD risk stratification should take into account the highest-risk status of patients with CKD.

The major goal of this statement is to review CKD as a risk factor for development of CVD. As background, we shall also review the definition of CKD and classification of stages of severity of CKD, the spectrum of CVD in CKD and differences from the general population, and risk factors for CVD in CKD.

Definition and Classification of Stages of Severity and Types of CKD

In 2002, the NKF published clinical practice guidelines on evaluation, classification, and risk stratification in CKD.[3] In these guidelines, CKD is defined as either (1) kidney damage for ≥3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR), or (2) GFR <60 mL · min^{-1} per 1.73 m^2 for ≥3 months, with or without kidney damage (Table 1).

Kidney damage is ascertained by either kidney biopsy or markers of kidney damage, such as proteinuria, abnormal urinary sediment, or abnormalities on imaging studies. The finding of proteinuria not only defines the presence of CKD but also has important implications for diagnosis of the type of kidney disease and is associated with a worse prognosis for both kidney disease progression and the development of CVD. Proteinuria is variously defined (Table 3).[3,19–21] Measurement of albumin-to-creatinine ratio or total protein-to-creatinine ratio in untimed "spot" urine samples is recommended for assessment of proteinuria.[3]

GFR <60 mL · min^{-1} per 1.73 m^2 is selected as the cutoff value for definition of CKD because it represents a reduction by more than half of the normal value of ≈125 mL · min^{-1} per 1.73 m^2 in young men and women, and this level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence and severity of several CVD risk factors. Estimation of GFR from serum creatinine and prediction equations including age, sex, race, and body size is recommended to avoid the

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in June 2003. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0258. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@heart.org. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

This statement is being copublished in the November 2003 issue of *Hypertension*.

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TABLE 1. Stages of CKD

Stage	Description	GFR, mL · min^{-1} per 1.73 m^2	US Prevalence, 1000s	US Prevalence, %
1	Kidney damage with normal or increased GFR	≥90	5900	3.3
2	Kidney damage with mildly decreased GFR	60–89	5300	3.0
3	Moderately decreased GFR	30–59	7600	4.3
4	Severely decreased GFR	15–29	400	0.2
5	Kidney failure	<15 or dialysis	300	0.1

Reproduced with permission from the National Kidney Foundation.[5]

Data for stages 1–4 from NHANES III (1988–1994), based on population of 177 million with age ≥20 years. Data for stage 5 from United States Renal Data System (1998)[1] include ≈230 000 patients treated by dialysis and assume 70 000 additional patients not on dialysis. GFR estimated from serum creatinine by abbreviated Modification of Diet in Renal Disease Study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >25 mg/g (women) on 2 measurements.

misclassification of individuals on the basis of serum creatinine alone[3,22–24] (Table 4 and NKF GFR calculator available at http://www.kidney.org/professionals/doqi/index.cfm).

Kidney failure is defined as GFR <15 mL · min^{-1} per 1.73 m^2 or treatment by dialysis. Approximately 98% of patients beginning dialysis for CKD in the United States have an estimated GFR of <15 mL · min^{-1} per 1.73 m^2.[25] This definition is not synonymous with end-stage renal disease, which is an administrative term in the United States signifying eligibility for coverage by Medicare for payment for dialysis and transplantation.

Among individuals with CKD, the stage of severity is based on the level of GFR (Table 1). The prevalence of kidney failure (≈300 000, or 0.1% of the US adult population) is considerably less than the prevalence of earlier stages of CKD (≈20 million, or 10.8% of the US adult population).

Diagnosis of CKD is traditionally based on pathology and etiology. A simplified classification, which we shall use in this article, emphasizes diseases in the native kidney, which can be broadly divided as diabetic and nondiabetic in origin, and kidney diseases in the transplant.[3,26,27]

Spectrum of CVD in CKD and Differences From the General Population

In this section, we consider arterial vascular disease and cardiomyopathy as the primary types of CVD (Table 4). In CKD, it is useful to consider 2 subtypes of arterial vascular disease, namely, atherosclerosis and large-vessel remodeling or arteriosclerosis. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions.[28] There is a high prevalence of atherosclerosis in CKD.[29,30] Atherosclerotic lesions in kidney failure are frequently calcified, as opposed to fibroatheromatous, and have increased media thickness compared with lesions in the general population.[31] Surrogates of atherosclerosis include both intima-media thickness of the carotid wall that is detectable by ultrasound and inducible myocardial ischemia that is detectable by coronary stress tests. Electron-beam computed tomography is a sensitive method to detect vascular calcification but may not be an ideal method to detect atherosclerosis in CKD, because it is unable to distinguish between intimal calcifications of atherosclerosis and medial calcification that is common in CKD. Clinical presentations of atherosclerosis include ischemic heart disease, namely,

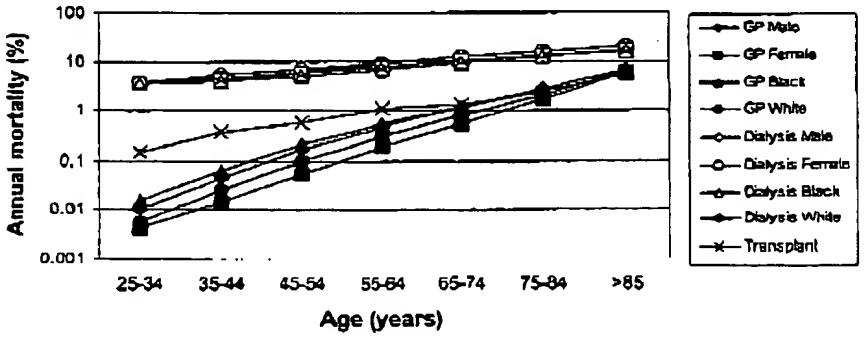

Figure 1. Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in general population (GP; National Center for Health Statistics [NCHS] multiple cause of mortality data files International Classification of Diseases, 9th Revision [ICD 9] codes 402, 404, 410 to 414, and 425 to 429, 1993) compared with kidney failure treated by dialysis or kidney transplant (United States Renal Data System [USRDS] special data request Health Care Financing Administration form 2746 Nos. 23, 26 to 29, and 31, 1994 to 1996). Data are stratified by age, race, and sex. CVD mortality is underestimated in kidney transplant recipients owing to incomplete ascertainment of cause of death. Reproduced and modified with permission from Foley et al.[6]

TABLE 2. Approximate Prevalence of CVD in the General Population and CKD

	Ischemic Heart Disease (Clinical)	LVH (Echo)	Heart Failure (Clinical)
General population	8–13*	20†	3–6‡
CKD stages 3–4 (diabetic and nondiabetic kidney disease)	NA	25–50 (varies with level of kidney function)§	NA
CKD stages 1–4 (kidney transplant recipients)	15‖	50–70¶	NA
CKD stage 5 (hemodialysis)	40#	75**	40#
CKD stage 5 (peritoneal dialysis)	40#	75**	40#

Reprinted and modified with permission from Foley et al.[9]

NA indicates not available. Values are percentages.

*Age 55–64 years. The higher percentage is for men. Data are from NHANES III, American Heart Association statistical Web site.[7]

†Data from Levy et al.[8]

‡Age 55–64 years. The higher percentage is for men. Data from NHANES III, American Heart Association statistical Web site.[7]

§Data from Levin et al.[9]

‖Data from Kasiske.[10]

¶Data from Parfrey et al,[11] Hernandez et al,[12] Peteiro et al,[13] Huting et al,[14] and Himelman et al.[15]

#Data from Dialysis Morbidity and Mortality (Wave 2). United States Renal Data System Annual Data Report, 1997.[16,17]

**Data from Foley et al.[18]

angina, myocardial infarction, and sudden cardiac death, which is common in CKD, and cerebrovascular disease, peripheral vascular disease, or heart failure (Table 5).

Stress imaging is an important modality for testing for myocardial ischemia. A recent meta-analysis reveals that stress imaging is of value in predicting CVD morbidity and mortality in kidney transplantation candidates treated by dialysis.[32] It remains unknown, however, whether the diagnostic accuracy of these tests, as defined by a "gold standard" of angiographic obstructive coronary artery disease, is different from the general population. Furthermore, it remains unknown whether stress nuclear or stress echocardiographic testing is more accurate in patients with CKD.

Dialysis patients with ischemic heart disease may not necessarily have large-vessel coronary disease. In one study, up to 50% of nondiabetic dialysis patients with symptoms of myocardial ischemia did not have large-vessel coronary artery disease (defined as luminal narrowing of >50% of major coronary vessels).[33] The authors hypothesized that the patients may have ischemia secondary to the combined effects of volume overload and left ventricular hypertrophy (LVH), which causes increased oxygen demand, and small-vessel coronary disease, which causes decreased oxygen supply. It needs to be acknowledged, however, that the latter study was performed in the pre-erythropoietin era, during which hemoglobin levels were lower, which also may have contributed to ischemia; therefore, the results may not be generalizable to current practice.

Patients with CKD also have a high prevalence of arteriosclerosis and remodeling of large arteries.[28] Remodeling may be due either to pressure overload, which is distinguished by wall hypertrophy and an increased wall-to-lumen ratio, or flow overload, which is characterized by a proportional increase in arterial diameter and wall thickness. Remodeling

TABLE 3. Definitions of Proteinuria

Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total protein			
24-Hour excretion (varies with method)	<300 mg/d	NA	≥300 mg/d
Spot urine dipstick	<30 mg/dL	NA	≥30 mg/dL
Spot urine protein-to-creatinine ratio (varies with method)	<200 mg/g	NA	≥200 mg/g
Albumin			
24-Hour excretion	<30 mg/d	30–300 mg/d	>300 mg/d
Spot urine albumin-specific dipstick	<3 mg/dL	>3 mg/dL	NA
Spot urine albumin-to-creatinine ratio (varies by sex*)	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

NA indicates not applicable.

*Sex-specific cutoff values are from a single study.[19] Use of the same cutoff value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cutoff values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to sex.[20]

Reproduced and modified with permission from the National Kidney Foundation.[3]

TABLE 4. Equations to Predict GFR Based on Serum Creatinine

Cockcroft-Gault equation[24]	$C_{Cr}(mL/min) = \frac{(140 - Age) \times Weight}{72 \times S_{Cr}} \times (0.85 \text{ if female})$
Abbreviated MDRD Study equation[22,23]	$GFR(mL \cdot min^{-1} \text{ per } 1.73\ m^2) = 186 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

C_{Cr} indicates creatinine clearance; MDRD, Modification of Diet in Renal Disease; and S_{Cr}, serum creatinine in mg/dL.

Age is given in years and weight in kilograms.

often accompanies a reduction in arterial compliance, which can be detected through measurement of aortic pulse wave velocity and characteristic impedance.[34,35] Noncompliant vessels may result in increased systolic blood pressure, increased pulse pressure, LVH, and decreased coronary perfusion. Both decreased aortic compliance[35–37] and increased pulse pressure[38] have been found to be independent risk factors for CVD in dialysis patients.

Patients with CKD also have a high prevalence of cardiomyopathy (Table 2).[18] Hypertension and arteriosclerosis result in pressure overload and lead to concentric LVH (increased wall-to-lumen ratio), whereas anemia, fluid overload, and arteriovenous fistulas result in volume overload and primarily lead to left ventricular dilatation with LVH (a proportional increase in left ventricular mass and diameter). These structural abnormalities may lead to diastolic and systolic dysfunction and may be detectable by echocardiography. Clinical presentations of cardiomyopathy include heart failure and ischemic heart disease, even in the absence of arterial vascular disease.

Diagnosis of heart failure may be challenging in dialysis patients because salt and water retention may be treated by ultrafiltration during dialysis, often leaving other signs and symptoms, such as decreased blood pressure, fatigue, and anorexia, as the only clues to its presence. On the other hand, salt and water retention may reflect inadequate ultrafiltration rather than heart failure or a combination of both heart failure and inadequate ultrafiltration. Indeed, one of the major causes of inadequate ultrafiltration during dialysis is hypotension, which may be a manifestation of heart failure. Regardless of the cause, heart failure is a powerful risk factor for adverse outcomes in dialysis patients, which suggests that it is usually a manifestation of advanced CVD.[39] Left ventricular mass index is dependent on volume status; therefore, there is a need for standardized assessments of left ventricular function in hemodialysis patients.[40]

CVD Risk Factors in CKD

In subjects with CKD, for the purposes of this discussion, we classify CVD risk factors as either "traditional" or "nontraditional" (Table 6),[41] and we define traditional risk factors as those in the Framingham Heart Study that have been used to estimate the risk of developing symptomatic ischemic heart disease.[42,43] Most of the traditional CVD risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low high-density lipoprotein (HDL) cholesterol, are highly prevalent in CKD. The cardiovascular risk conferred by many traditional risk factors, such as diabetes,[6] older age,[2] and LVH,[44] largely parallels the relationships described in the general population, although some important differences have been noted with regard to other risk factors. For example, U-shaped relationships exist between all-cause mortality and both blood pressure and cholesterol levels in dialysis patients (Figure 2).[45–48] The increased risk at lower levels of blood pressure and cholesterol may reflect confounding from cardiomyopathy and malnutrition, respectively, although this has not been proved. In support of the latter, hypertension was a risk factor for the development of LVH, heart failure, and ischemic heart disease but not mortality in a Canadian cohort of dialysis patients.[49]

Several cross-sectional studies have suggested that the Framingham risk equation is insufficient to capture the extent of CVD risk in subjects with CKD.[17,50,51] There are 2 interpretations for these findings. First, other factors (nontraditional risk factors) that are not included in Framingham risk equations may play an important role in promoting ischemic

TABLE 5. Spectrum of CVD in CKD: Differences From the General Population

Types of CVD/Pathology	Surrogates	Clinical Presentations of CVD
Arterial vascular disease		
Atherosclerosis	Inducible ischemia, carotid IMT, EBCT (may be less useful than in the GP for atherosclerosis because of medial rather than intimal calcification), ischemia by ECG	IHD (myocardial infarction, angina, sudden cardiac death), cerebrovascular disease, PVD, HF
Arteriosclerosis: dilated and noncompliant large vessels	Aortic pulse wave velocity, calcification of the aorta, LVH (indirectly), increased pulse pressure	IHD, HF
Cardiomyopathy		
Concentric LVH and LV dilatation with proportional hypertrophy	LVH, systolic dysfunction, and diastolic dysfunction by echocardiogram. LVH by ECG	HF, hypotension, IHD

IMT indicates intima-media thickness; EBCT, electron-beam computed tomography; GP, general population; ECG, electrocardiogram; IHD, ischemic heart disease; PVD, peripheral vascular disease; HF, heart failure; and LV, left ventricular.

TABLE 6. Traditional and Nontraditional Cardiovascular Risk Factors in CKD

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
LVH	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
Reproduced and modified with permission from Sarnak et al.[41]

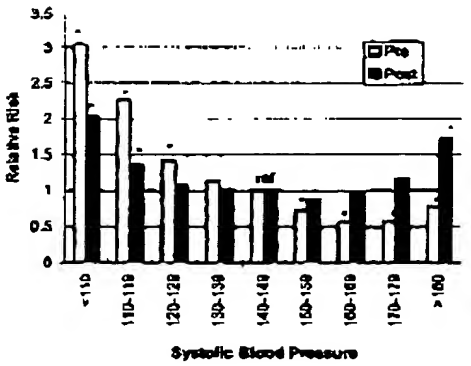

Figure 2. Mortality vs systolic blood pressure in hemodialysis patients. Dialysis Clinic, Inc prevalent cohort (1992 to 1996; n=5433). Cox regression analysis including age, race, sex, and diagnosis as baseline covariates and predialysis (Pre) or postdialysis (Post) systolic blood pressure, albumin, and Kt/V as time-dependent covariates. Reproduced with permission from Zager et al.[46]

heart disease in subjects with CKD. Second, traditional risk factors may have a qualitatively and quantitatively different risk relationship with CVD in CKD compared with the general population. For example, individuals with CKD may have had a longer and more severe exposure to hypertension than subjects without CKD. In addition, subjects with CKD may have been treated for hypertension, and the Framingham risk equation does not take into account dose or years of treatment with antihypertensive medications.[52]

To define a nontraditional factor as a risk factor, all of the following conditions ideally should be met: (1) biological plausibility as to why the factor may promote CVD risk; (2) demonstration that the risk factor level increases with severity of kidney disease; (3) demonstration of an association between the risk factor and CVD in CKD in observational studies; and (4) demonstration in placebo-controlled clinical trials that treatment of the risk factor decreases CVD outcomes. Although conditions 1 and 2 are met for the most part when one considers the nontraditional risk factors listed in Table 6, there remain many gaps in the CKD literature regarding condition 3, and particularly condition 4. This is, therefore, an active area of research.

Several nontraditional factors, such as hyperhomocysteinemia, oxidant stress, dyslipidemia, and elevated inflammatory markers, are associated with atherosclerosis,[53–60] and 2 recent reviews suggest that oxidant stress and inflammation may be the primary mediators or the "missing link" that explains the

TABLE 7. Microalbuminuria as a Risk Factor for CVD Outcomes in Subjects With Diabetes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Stehouwer, 2002[95]	Type 2 DM; age <66 y	363	NA	NA	+
Gerstein, 2001[60]	DM plus another CVD risk factor	3498	Composite: MI, stroke, CVD death	+	+
Agewall, 1997[96]	DM and treated hypertension	94	CVD mortality	+	+
Stephenson, 1995[84]	Type 1 DM	1188	CVD mortality	+	+
Stephenson, 1995[84]	Type 2 DM	3234	CVD mortality	+	+
Dinneen, 1997[90]	Type 2 DM: pooled odds ratios of 11 cohort studies	2138	Composite: CVD morbidity and mortality	+	+
Mogensen, 1984[91]	Type 2 DM; age 50–75 y	76	NA	NA	+
Valmadrid, 2000[97]	Type 2 DM; mean age 68 y	840	CVD mortality	+	+
Miettinen, 1996[93]	Type 2 DM	1056	Composite: stroke, IHD, and PVD	+	NA
Messent, 1992[92]	Type 1 DM	63	CVD mortality	+	–
Rossing, 1996[94]	Type 1 DM	939	CVD mortality	+	+
Gall, 1995[89]	White with type 2 DM	329	CVD mortality	–*	+
Uusitupa, 1993[98]	Incident type 2 DM	133	CVD mortality	–	NA

DM indicates diabetes mellitus; NA (no data available), the outcome was not evaluated in the study; MI, myocardial infarction; IHD, ischemic heart disease; PVD, peripheral vascular disease; +, the author concluded that microalbuminuria was an independent risk factor for the outcome after adjustment for all other CVD risk factors; and –, the author concluded that microalbuminuria was not an independent risk factor for the outcome after adjustment for all other CVD risk factors.

*Macroalbuminuria but not microalbuminuria was an independent risk factor.

All subjects are considered highest risk in this table because by definition, subjects had diabetes. Only prospective studies are considered.

tremendous burden of CVD in CKD.[61,62] Other factors such as anemia are associated with cardiomyopathy,[9,63] whereas abnormal calcium and phosphorus metabolism is associated with vascular remodeling and development of noncompliant vessels.[64]

As mentioned above, although many of these putative risk factors are associated with increased risk for either all-cause mortality or CVD in various stages of CKD,[56,57,65–68] for the most part, their causal relationship to CVD has not yet been proved in clinical trials. However, 3 important clinical trials include the following. The Normal Hematocrit Trial enrolled ≈1300 hemodialysis patients with ischemic heart disease or heart failure and randomized them to a predialysis hematocrit goal of either 30% or 42% with the use of erythropoietin.[69] The higher hematocrit group had a higher (although not significantly) incidence of all-cause mortality and myocardial infarction, the primary end point. The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE) Study randomized 196 hemodialysis patients with CVD to 800 U of vitamin E or placebo. The vitamin E group had a lower incidence of the primary end point, which was a composite of myocardial infarction (both fatal and nonfatal), ischemic stroke, peripheral vascular disease, and unstable angina.[70] Finally, a recent controlled trial randomized 134 hemodialysis patients to either 600 mg of oral acetylcysteine (an antioxidant) twice per day or placebo.[71] Those patients randomized to acetylcysteine had a lower incidence of the primary end point, which was a composite of fatal and nonfatal myocardial infarction, CVD death, need for coronary angioplasty or coronary artery bypass surgery, ischemic stroke, and peripheral vascular disease manifested by either amputation or need for angioplasty. Although the latter 2 studies should be interpreted with caution because they were small and are not consistent with studies in the general population,[72] it is important to recognize that dialysis patients have higher levels of oxidant stress and inflammation than the general population: therefore, the results are provocative and need to be followed up in larger trials.

CVD in Kidney Failure

CVD mortality is ≈10 to 30 times higher in patients treated by dialysis than in patients in the general population, despite stratification for sex, race, and the presence of diabetes.[6] After stratification for age, CVD mortality remains ≈5-fold higher in dialysis patients than in the general population, even at the extremes of age (Figure 1). The high mortality rate is likely due to both a high case fatality rate and a high prevalence of CVD.

A high case fatality rate in dialysis patients has been observed after acute myocardial infarction and in patients with heart failure. Mortality 1 and 2 years after myocardial infarction was 59% and 73%, respectively, in dialysis patients (Figure 3),[73] which is much higher than after acute myocardial infarction in the general population, even in subjects with comorbid conditions such as diabetes. For example, in the Worcester Heart Attack Study, approximately three fourths of diabetic men and two thirds of diabetic women discharged after an acute myocardial infarction were still alive 2 years later.[74] In another study in dialysis patients, median survival was only 18 months after development of de novo heart failure, which is also far higher than observed in the general population.[30]

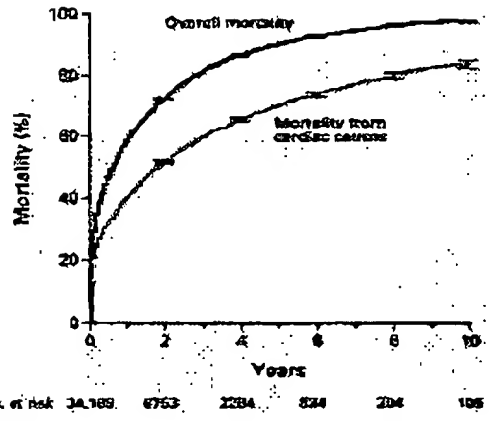

Figure 3. Estimated cumulative mortality after acute myocardial infarction among patients on dialysis. Reproduced with permission from Herzog et al.[73]

The prevalences of atherosclerosis, heart failure, and LVH are extremely high in hemodialysis patients (Table 2).[6] Approximately 40% of incident hemodialysis patients have clinical evidence of ischemic heart disease or heart failure. In addition, the prevalence of LVH in incident dialysis patients is high. In the Canadian Prospective Cohort Study of 433 incident dialysis patients, 74% had LVH at baseline, 44% had concentric LVH, 30% had hypertrophy with left ventricular dilatation, and 15% had systolic dysfunction.[18]

CVD in Kidney Transplant Recipients

CVD accounts for 35% to 50% of all-cause mortality in kidney transplant recipients,[75–77] and CVD mortality rates are at least twice as high as in an age-stratified sample of the general population but significantly lower than an age-stratified dialysis population (Figure 1).[6,77] The 2 most likely explanations for the reduced risk in kidney transplant recipients compared with dialysis patients are selection bias for those undergoing transplantation and removal of the hemodynamic and uremic abnormalities associated with dialysis in those who receive transplants.

CVD morbidity is also higher in transplant recipients than in the general population even in comparisons with population samples with similar age and sex distributions. The prevalence of coronary artery disease is ≈15%,[10] the prevalence of LVH is 50% to 70%,[11–15] and the incidence of CVD is at least 3 to 5 times that of the general population.[6,10]

Risk factors for CVD in kidney transplant recipients are multiple. They include traditional CVD risk factors, such as hypertension, diabetes, hyperlipidemia, and LVH, which are highly prevalent, and nontraditional risk factors associated with reduced GFR, such as hyperhomocysteinemia or factors unique to transplantation itself, including the direct effects of immunosuppression or rejection. It has recently been demonstrated that although the Framingham risk equation predicts ischemic heart disease after kidney transplantation, it tends to

TABLE 8. Proteinuria as a Risk Factor for CVD Outcomes in Patients Without Diabetes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Highest-risk population					
Gerstein, 2001[80]	Vascular disease	5545	Composite: MI, stroke, CVD mortality	+	+
Diercks, 2002[112]	Subjects with ST-T–wave changes	7330	CVD mortality	+	+
High-risk populations					
De Leeuw, 2002[171]	Systolic hypertension and age ≥60 y	4695	Composite: fatal and nonfatal CVD (stroke and IHD)	+	+
Ljungman, 1996[115]	Hypertensive and nonhypertensive men	120	Composite: IHD, stroke, and PVD	+	NA
Agewall, 1997[88]	Treated hypertension	345	CVD mortality	–	–
Damsgaard, 1990[113]	Age 60–74 y	216	NA	NA	+
Grimm, 1997[114]	Men in the upper 15% of coronary heart disease risk	12 866	CVD mortality	+	+
Yudkin, 1988[124]	Diabetic screening project	187	NA	NA	+
Culleton, 1998[110]	Men with mean age 68 y	1045	CVD mortality	–	+
Culleton, 1998[170]	Women with mean age 69 y	1541	CVD mortality	+	+
Jager, 1999[117]	Age 50–75 y stratified by glucose tolerance	631	CVD mortality	+	+
Roest, 2001[121]	Postmenopausal women	561 cases, 557 controls*	CVD mortality	+	NA
Kuusisto, 1995[120]	Mean age 68 y	1069	IHD death and nonfatal MI	+	NA
Ordonez, 1993[122]	Nephrotic syndrome	142 cases, 142 controls*	Composite: MI, angina and coronary insufficiency	+	+
Low-risk populations					
Hillege, 2002[116]	City of Groningen	40 458	CVD mortality	+	+
Miettinen, 1996[83]	Finnish cohort	1375	Composite: IHD, stroke, and PVD	+	NA
Wagner, 1994[123]	White men aged 45–74 y, NHANES I	6588	CVD mortality	+	+
Wagner, 1994[125]	White women aged 45–74 y, NHANES I	6588	CVD mortality	–	+
Mumtner, 2002[118]	NHANES II	6534	CVD mortality	+	+
Kannel, 1984[118]	Framingham men	5209	CVD mortality	+	+
Kannel, 1984[119]	Framingham women	5209	CVD mortality	–	–

+ indicates that the author concluded that proteinuria was an independent risk factor for the outcome after adjustment for all other risk factors; –, the author concluded that proteinuria was not an independent risk factor for the outcome after adjustment for all other risk factors. All other abbreviations as in Table 7.

*Case-control studies. All the rest of the studies in the table are prospective studies.

Populations were considered highest risk if they had CVD, other vascular disease, surrogates of CVD, or diabetes; high risk if subjects were selected on the basis of having a traditional CVD risk factor such as hypertension or increased age; and low risk if the population was a community study.

underestimate the risks, especially the risk associated with diabetes.[78] The latter effect is probably due to more severe diabetic vascular disease in patients with diabetic kidney disease.

CVD in Diabetic Kidney Disease

In this section, we primarily focus on microalbuminuria, because it is the earliest sign of kidney disease in diabetes. We define all patients as being in the highest risk group for future CVD events because of the presence of diabetes.

Microalbuminuria is associated with an increased prevalence of CVD risk factors. Although blood pressure may be normal in subjects with type 1 diabetes, a pattern of "nondipping" at night is frequently observed by 24-hour ambulatory blood pressure monitoring and may precede the development of microalbuminuria.[79] Nondipping is a well-recognized CVD risk factor. Diabetic subjects with microalbuminuria also have an increased prevalence of dyslipidemia, poor glucose control, and increased blood pressure compared with diabetic patients without microalbuminuria.[80,81]

There is a strong association between microalbuminuria (albuminuria) and CVD in cross-sectional analysis. This relationship has been found for surrogate measures, such as carotid intima-media thickness[82] and LVH,[83,84] and different clinical presentations of CVD, such as coronary artery disease[81,84] and peripheral vascular disease.[85] The relationship between microalbuminuria (albuminuria) and clinical CVD has been confirmed in diverse racial/ethnic groups, including Koreans, American Indians, and Asian Indians.[81,86,87] Although the relationship is present in both type 1 and type 2 diabetes, the relationship is generally stronger in type 2 diabetes because of the older age of individuals with this disease.

TABLE 9. Decreased GFR as a Risk Factor for CVD Outcomes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Highest-risk populations					
Dries, 2000[149]	Ejection fraction ≤35%	5834	Pump failure mortality	+	+
Kearney, 2002*[150]	Ambulatory patients with chronic HF	553	Mortality due to progressive HF	+	+
McClellan, 2002[152]	HF by ICD 9 code	665	NA	NA	+
Hillege, 2000[151]	Class III and IV NYHA HF and LVEF <35%	1906	NA	NA	+
Mahon, 2002[153]	HF	585	NA	NA	+
McCullough, 2000[138]	CCU	9544	Arrhythmias, conduction problems, HF, shock, mitral regurgitation	+	+
Soman, 2002[141]	CCU	9544	Arrhythmias	+	NA
Matts, 1993[142]	MI	417	CVD mortality	+	+
Walsh, 2002[143]	MI	483	NA	NA	+
Beattie, 2001[146]	MI	1724	NA	NA	+
Shlipak, 2002[148]	Elderly and MI	130 099	NA	NA	+*
Wright, 2002[161]	MI	3106	NA	NA	+
McCullough, 2002[140]	Emergency department with possible MI	808	Composite: all-cause mortality, MI, HF	+	NA
Al Suwaidi, 2002[157]	Acute coronary syndromes	37 925	Composite: all-cause mortality and MI	+	+
Freeman, 2003[173]	Acute coronary syndromes	889	NA	NA	+
Wison, 2003[174]	Acute coronary syndromes	2503	CVD mortality	+	NA
Januzzi, 2002[160]	Non–ST-elevation coronary syndrome	1570	Composite: all-cause mortality, MI, and refractory ischemia	+†	NA
Best, 2002[156]	PCI	5327	NA	NA	+
Snaw, 2002[166]	PCI	100 253	CVD mortality	−	+
Rubenstein, 2000[144]	PCI	3334	Composite: all-cause mortality, MI, CABG, and repeat PCI	+	+
Reinecke, 2003[177]	PCI	1049	NA	NA	+
Szczech, 2001[154]	CABG or PCI	59 576	NA	NA	+
Szczech, 2002[155]	CABG or PCI	3608	CVD mortality	+	+
Gruberg, 2002[158]	Coronary stents	5084	NA	NA	+
Gruberg, 2003[172]	PCI with saphenous vein grafts	1265	NA	NA	+
Anderson, 1999[179]	CABG	3902	Composite: cardiac arrest and HF	+	+
Beddhu, 2002[159]	Coronary angiography	8600	MI	+	+
Hemmelgarn, 2001[145]	Coronary angiography	16 989	NA	NA	+
Shlipak, 2001[147]	Postmenopausal women with coronary disease	2763	Composite: IHD and stroke	+	NA
Mann, 2001[137]	Vascular disease or diabetes combined with another CVD risk factor	9297	Composite: CVD mortality, MI, and stroke	+	+‡
Anderson, 2000[175]	Valve surgery	834	Composite: cardiac arrest and low cardiac output	+	+
High-risk populations					
Fried, 1998[162]	Age ≥65 y	5201	NA	NA	+
Manjunath, 2003[137]	Age ≥65 y	4893	Composite: HF, IHD, PVD, stroke, and CVD mortality	+	+
Manolio, 1996[163]	Age ≥65 y	5201	Stroke	+	NA
Gottdiener, 2000[164]	Age ≥65 y	5888	HF	+	NA
Rullope, 2001[134]	Hypertension	18 597	Composite: CVD death, MI, and stroke	+	+
Schillaci, 2001[165]	Whites with hypertension	1829	Composite: IHD, TIA, stroke, HF, and symptomatic aortoiliac disease	+	−
De Leeuw, 2002[111]	Isolated systolic hypertension and age ≥60 y	4695	Fatal and nonfatal CVD (stroke and IHD)	+	+
Henry, 2002[165]	Age 50 to 75 y and 27% DM by design	631	CVD mortality	+	+
Flack, 1993[167]	Hypertensive men	5524	CVD mortality	−	−
Shulman, 1989[4]	Hypertension	10 940	CVD	+	+
O'Brien, 2002[169]	General surgery; mean age 60 y	49 081	Cardiac arrest	+	+
Low-risk populations					
Garg, 2002[170]	NHANES I	2352	CVD mortality	−	−
Muntner, 2002[119]	NHANES II	6534	CVD mortality	+	+
Culleton, 1999[131]	Men	2837	Composite: CVD death, HF, IHD, and stroke	−	+
Culleton, 1999[131]	Women	3388	Composite: CVD mortality, HF, IHD, and stroke	−	−

TABLE 9. Continued

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Manjunath, 2003[139]	Age 45–65 y	15 350	Composite: CVD mortality, stroke, and IHD	+	NA
Wannamethee, 1997[171]	Men 40–59 y	7690	Stroke	+	+
Wannamethee, 1997[171]	Men 40–59 y	7690	IHD	−	+

HF indicates heart failure; ICD 9, International Classification of Diseases, 9th revision; NA (no data available), the outcome was not evaluated in the study; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CCU, coronary care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; IHD, ischemic heart disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; DM, diabetes mellitus; +, the author concluded that decreased GFR was an independent risk factor for the outcome after adjustment for all other risk factors; and −, the author concluded that GFR was not an independent risk factor for the outcome after adjustment for all other risk factors.

*Positive for 6-month follow-up and negative for 1-year follow-up.

†Not adjusted.

‡Adjusted only for center.

Studies whose primary goal was to evaluate whether CKD is a risk factor for acute kidney failure are not included in this table. Only prospective studies are considered in this table. Populations were considered highest risk if they had CVD, other vascular disease, surrogates of CVD, or diabetes; high risk if subjects were selected on the basis of having a traditional CVD risk factor; and low risk if they were community studies.

Longitudinal studies also document that microalbuminuria is an adverse prognostic indicator for clinical CVD outcomes and all-cause mortality in subjects with diabetes (Table 7).[80,84,88–97] For example, in the Heart Outcomes Prevention Evaluation (HOPE) Study (subjects with vascular disease or diabetes plus another traditional risk factor at baseline), those with microalbuminuria and diabetes had a 1.97-fold (95% confidence interval 1.68 to 2.31) and 2.15-fold (95% confidence interval 1.78 to 2.60) increased risk for a composite outcome of myocardial infarction, stroke, or CVD death, as well as all-cause mortality, respectively, compared with subjects with diabetes without microalbuminuria.[80] A recent pooled analysis of type 2 diabetes in 11 cohort studies (2138 patients followed up for a mean of 6.4 years) showed that microalbuminuria was associated with an adjusted overall odds ratio for all-cause mortality of 2.4 (95% confidence interval 1.8 to 3.1) and for cardiovascular morbidity and mortality of 2.0 (95% confidence interval 1.4 to 2.7).[90]

There are several potential explanations for why the presence of microalbuminuria may be a risk factor for outcomes in diabetes. First, as discussed above, subjects with microalbuminuria have a higher prevalence of traditional risk factors than diabetic subjects without microalbuminuria. However, even after adjustment for other risk factors, the presence of microalbuminuria remains an adverse prognostic indicator (Table 7). Second, microalbuminuria may reflect generalized endothelial dysfunction and increased vascular permeability or abnormalities in the coagulation and fibrinolytic systems.[98,99] Third, microalbuminuria may be associated with inflammatory markers.[100] Fourth, microalbuminuria may denote the greater severity of end organ damage. Therefore, even if one adjusts for the presence of clinical CVD, the subject with microalbuminuria likely has more advanced disease.

CVD in Nondiabetic Kidney Disease

In this section, we focus on proteinuria and reduced GFR as manifestations of CKD. We consider proteinuria rather than microalbuminuria alone because studies have evaluated microalbuminuria, albuminuria, dipstick proteinuria, or nephrotic range proteinuria. Nephrotic syndrome in diabetic and nondiabetic individuals is associated with a number of disorders that have been implicated in CVD, such as extreme dyslipidemia and hypercoagulability, and is reviewed elsewhere.[101,102] The goal of this review is to highlight the importance of lower levels of proteinuria.

We define a highest-risk population as one that is selected for already having CVD, other vascular disease, surrogates of CVD (such as LVH), or diabetes. An intermediate-risk population is one that is selected for having a traditional risk factor for CVD, such as increased age or hypertension. A low-risk population was defined as a community study.

Proteinuria

As in subjects with diabetes, nondiabetic persons with microalbuminuria have a higher prevalence of CVD risk factors (including dyslipidemia, increased blood pressure by 24-hour ambulatory blood pressure monitoring, heavier body size, insulin resistance, and a history of smoking) than subjects without microalbuminuria.[103–105] There is a strong association between microalbuminuria and CVD in cross-sectional analysis. For example, microalbuminuria is associated with surrogates of CVD, such as increased intima-media thickness of the carotid artery in hypertensive subjects,[106] more frequent concentric LVH in hypertensive men,[104] abnormal left ventricular geometry and mass in subjects with hypertension and LVH,[107,108] and electrocardiographic evidence of myocardial ischemia.[109] Subjects with microalbuminuria also have a higher prevalence of clinical CVD than those without microalbuminuria.[105]

As in subjects with diabetic kidney disease, the presence of proteinuria in nondiabetic individuals is, for the most part, independently associated with an increased risk for CVD events in longitudinal studies (Table 8).[80,88,93,110–124] Microalbuminuria in nondiabetic subjects in the HOPE study was associated with a 61% increased risk of the composite end point of stroke, myocardial infarction, or CVD death and a 2-fold increase in risk for all-cause mortality.[80] In low-risk populations, however, the results have been less consistent. For example, in the Framingham Heart Study, the relative

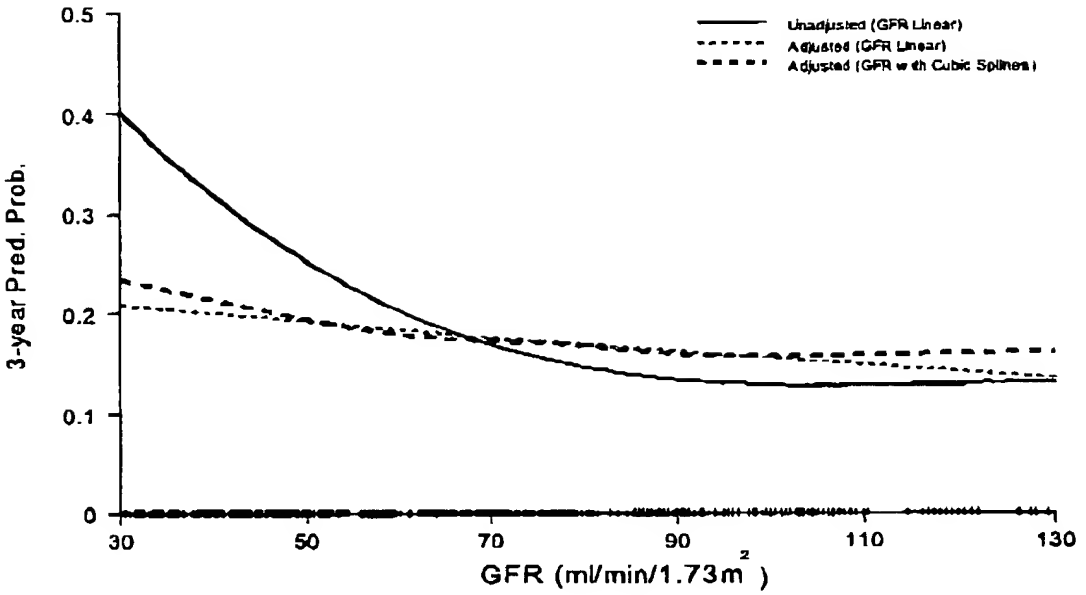

Figure 4. Smoothed 3-year predicted probability (Pred. Prob.) of developing CVD by level of GFR in the Cardiovascular Health Study. Unadjusted curve shows risk incorporating each individual's value for other covariates. Adjusted curve shows average risk in population if everyone had GFR value shown on x-axis. Linear model includes GFR as continuous variable in Cox regression, whereas cubic spline includes cubic transition between linear segments with knots (at 0.05, 0.275, 0.5, 0.725, 0.95 quantiles of GFR) corresponding to GFR values of 45.3, 64.0, 76.2, 88.5, and 107.3 mL · min^{-1} per 1.73 m^2, respectively. Tick marks along the x-axis indicate GFR values for individual participants with events (marks form solid bar in GFR regions with many events). Lower GFR cutoff of 30 mL · min^{-1} per 1.73 m^2 was chosen because only 37 subjects had GFR values between 15 and 30 mL · min^{-1} per 1.73 m^2; therefore, data were less precise in latter range. Reproduced and modified with permission from Manjunath et al.[137]

risk for CVD death or all-cause mortality for dipstick-positive proteinuria in women was similar to that in the HOPE study, but there was no significant independent association between dipstick-positive proteinuria and these outcomes in men.[110] Conversely, in the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study, a community study in the Netherlands, a doubling of urine albumin concentration was associated with a 29% increase in relative risk for CVD mortality.[116] As in diabetic kidney disease, the presence of microalbuminuria in nondiabetic individuals may reflect generalized endothelial dysfunction[125–129] or abnormalities of the fibrinolytic and coagulation pathways, may be a marker of inflammatory status,[130] or may denote the greater severity of the target end-organ damage.

Reduced GFR

Reduced GFR is associated with a high prevalence of CVD risk factors and a higher prevalence of CVD surrogates and clinical CVD. For example, several studies across a broad spectrum of populations, such as the HOPE study, the Cardiovascular Health Study (CHS), the Hypertension Optimal Treatment (HOT) Study, the Framingham and Framingham Offspring Studies, and the Atherosclerosis Risk In Communities (ARIC) Study, have shown that levels of systolic blood pressure and total cholesterol and the percentage of subjects with low HDL cholesterol are greater in subjects with decreased GFR. In addition, the percentages of subjects with diabetes, electrocardiographic LVH, ischemic heart disease, and heart failure are higher in those with decreased GFR.[131–135] More recently, it has been demonstrated that the level of kidney function is also associated with the extent of demonstrable angiographic coronary disease. For example, in women with chest pain who undergo angiography, an elevated creatinine of 1.2 to 1.9 mg/dL is an independent predictor of significant angiographic coronary disease, as defined by a luminal narrowing of 50%.[136]

The prevalence of LVH is also inversely related to the level of GFR. In one study, the prevalence of LVH, as measured by echocardiography, was 45%, 31%, and 27% in patients with creatinine clearance of <25, 25 to 50, and >50 mL/min, respectively.[9] These percentages contrast sharply with the <20% prevalence of LVH in similar-aged patients in the general population.[8]

Reduced GFR is also associated with clinical CVD outcomes in prospective studies. It is important initially to consider the effect of reduced GFR on CVD outcomes without adjustment for other risk factors for 2 reasons. First, decreased GFR may be associated with other CVD risk factors and therefore may be useful for risk stratification in and of itself. Second, the adjusted analyses may inappropriately reduce the association between level of GFR and outcomes. That is, reduced GFR may result in more severe hypertension and dyslipidemia, and therefore one may overcorrect for effects if factors in the causal pathway of lower GFR to CVD are included in statistical adjustments. Figure 4 demonstrates the difference in the probability of developing CVD over 3 years by level of GFR with and without adjustment for other CVD risk factors in the CHS.[137] Without

adjustment for other risk factors, a GFR of 30 mL · min^{-1} per 1.73 m^2 is associated with a CVD risk of 40%, compared with 15% associated with a GFR of 130 mL · min^{-1} per 1.73 m^2. After adjustment for other CVD risk factors, a GFR of 30 mL · min^{-1} per 1.73 m^2 is associated with a CVD risk of 22%, compared with 15% associated with a GFR of 130 mL · min^{-1} per 1.73 m^2. The interpretation of this finding is that although much of the risk of CKD is due to its association with other CVD risk factors, the presence of CKD in and of itself remains an important independent risk factor for CVD outcomes.

Decreased GFR has consistently been found to be an independent risk factor for CVD outcomes and all-cause mortality in the highest-risk populations (Table 9).* This is true in subjects with vascular disease or diabetes plus another CVD risk factor, after coronary artery bypass, after cardiac valve surgery, after myocardial infarction, in patients undergoing percutaneous coronary interventions, in patients with unstable coronary syndromes, in patients presenting to the emergency ward with chest pain, and in patients with heart failure.† Furthermore, it appears that this increase in risk is present with even mild reduction in kidney function.[174,177,178]

In high-risk populations, most but not all studies have suggested that decreased GFR is an independent risk factor for outcomes. This is true in the elderly, in whom even mild reductions of kidney function are associated with worse outcomes,[137] in studies of subjects with hypertension,[4] in studies of populations with a higher than normal prevalence of diabetes,[165] and among older patients undergoing general surgery.[169] In the Multiple Risk Factor Intervention Trial (MRFIT), the baseline creatinine level was not independently associated with CVD outcomes or all-cause mortality. However, an increase in follow-up serum creatinine level at 6 years did predict adverse CVD outcomes.[167] The authors postulated that the lack of association with baseline serum creatinine may have been due to a narrow range of serum creatinine levels at baseline.

In low-risk populations or community studies, the relationship between the level of kidney function and outcomes has not been as clear. In both the Framingham Study and the first National Health And Nutrition Examination Survey (NHANES I), the level of kidney function was not an independent risk factor for CVD outcomes,[131,170] whereas in the ARIC Study and NHANES II, it was a risk factor for both CVD and all-cause mortality.[119,132] Potential reasons for the discrepancies in the studies include differences in the study populations (for example, blacks were part of the ARIC study but not the Framingham studies), alternate measures to ascertain level of kidney function (serum creatinine is less sensitive than estimated GFR to detect small differences in level of kidney function and therefore may be less likely to detect an association in a low-risk population), and potential type II errors due to lower CVD event rates in community studies.[179] Either way, it appears that the presence of reduced GFR is either not a risk factor or at most is a modest independent risk factor for CVD outcomes in low-risk populations.

*References 4, 111, 119, 131–134, 137–177.
†References 132, 135, 139, 140, 144–146, 149, 155, 161, 175, 176.

There are a number of possible explanations for the independent association of reduced GFR and CVD outcomes. First, a reduced GFR may be associated with an increased level of nontraditional CVD risk factors that frequently are not assessed in many studies.[180,181] Second, reduced GFR may be a marker of undiagnosed vascular disease or alternatively a marker for the severity of diagnosed vascular disease, especially in high- or highest-risk populations. Third, reduced GFR may be a measure of residual confounding from traditional CVD risk factors. For example, subjects with reduced GFR may have had more severe hypertension or dyslipidemia and therefore have suffered more vascular damage secondary to hypertension or dyslipidemia. Fourth, recent studies have suggested that subjects with reduced GFR are less likely to receive medications or therapies such as angiotensin converting enzyme inhibitors, β-blockers, aspirin, platelet inhibitors, thrombolytics, or percutaneous intervention than patients with preserved GFR. Perhaps as important was the fact that in the same studies, patients with reduced GFR who did receive the above interventions obtained similar benefit as patients with preserved GFR.[146,148,161,173,182,183] Finally, decreased GFR itself may be a risk factor for progression of ventricular remodeling and cardiac dysfunction.

The results in Tables 7 through 9 may be limited for the following reasons. First, negative results may not have been submitted or published, resulting in a publication bias. Second, we did not perform a systematic review to locate all studies for which the primary goal was the evaluation of the relationship between either proteinuria (albuminuria) or reduced GFR and CVD outcomes. Third, there is a possibility that other studies of which we are not aware evaluated risk factors for CVD outcomes and included proteinuria (microalbuminuria) or level of kidney function in the multivariable analyses. Finally, we have not included studies for which the primary goal was the evaluation of risk factors for acute kidney failure—for example, after receiving intravenous contrast agents. These studies may be relevant, because reduced GFR is a strong risk factor for acute kidney failure and through this mechanism may lead to an increase in CVD events and all-cause mortality.[184]

Unanswered Questions

There remain many unanswered questions. A few, alluded to above, include the following: Are all the potential nontraditional risk factors defined in Table 6 indeed risk factors for CVD in all stages of CKD? Is a mild decrease in GFR associated with an increased CVD risk in low-risk populations, and if so, through what mechanism? Will therapy designed specifically to reduce albuminuria/proteinuria decrease CVD events? What are the cellular mechanisms of left ventricular remodeling in CKD, and how may treatment modalities alter this process? We also expand on 2 additional questions.

First, is the presence of CKD more of a risk factor for heart failure or ischemic heart disease outcomes? There is debate in the literature whether the presence of CKD leads primarily to accelerated atherosclerosis with manifestations of ischemic heart disease or cardiomyopathy manifested primarily as heart failure. A recent study in kidney transplantation patients has shown that the incidence of de novo heart failure was

considerably higher in kidney transplant recipients than in the Framingham cohort, whereas the incidence of ischemic heart disease was not.[185] However, because most studies have not clearly distinguished between the risk of heart failure versus the risk of ischemic heart disease, this issue remains unresolved and needs additional study.

Second, is there a threshold level of GFR below which an increased risk for CVD begins or where the risk for CVD increases in a nonlinear fashion? Many studies have suggested that the relative risk for CVD increases more rapidly below a GFR of ≈60 mL · min^{-1} per 1.73 m^2 [133,137,139,148,159]; however, formal statistical analyses have not had sufficient power to prove this point.[133,137] In theory, a threshold level of GFR of ≈60 mL · min^{-1} per 1.73 m^2 may make sense, because the prevalence of many nontraditional risk factors, such as anemia and abnormalities of calcium and phosphorus metabolism, increases as GFR decreases below this range.

Summary

There is a high prevalence of CVD in subjects with CKD. The presence of CKD, whether it is manifested by proteinuria (albuminuria) or reduced GFR, appears to be an independent risk factor for CVD outcomes, particularly in higher-risk populations. These findings are consistent with the NKF task force recommendation that patients with CKD should be considered in the highest-risk group for CVD events. The seventh report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) includes CKD as a "compelling" indication, justifying lower target blood pressure and treatment with specific antihypertensive agents.[186] Similarly, the recently published "NKF-K/DOQI Clinical Practice Guidelines on Managing Dyslipidemia in Chronic Kidney Disease" recommend that all patients with CKD be included in the highest-risk group, justifying a lower target low-density lipoprotein cholesterol level.[53] By contrast, the third report of the Adult Treatment Panel of the National Cholesterol Education Program (ATP-III) does not include CKD in the list of high-risk conditions necessitating more aggressive management.[187] We suggest that the National Cholesterol Education Program and other groups include CKD in the highest-risk group for recommendations for prevention, detection, and treatment of CVD risk factors. In addition, these findings reinforce the recent recommendation from the NKF on the importance of early identification and treatment of CKD and its associated comorbid conditions. We suggest that the routine evaluation of patients with CVD or those at high risk for CVD include measurement of spot urine albumin-to-creatinine ratio or total protein-to-creatinine ratio and estimation of GFR by serum creatinine and prediction equations. Finally, there is an urgent need for additional randomized controlled studies to evaluate potential treatments of CVD in CKD.

References

1. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *US Renal Data System. USRDS 1998 Annual Data Report*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1998. Available at: http://www.usrds.org/adr_1998.htm. Accessed September 12, 2003.
2. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *US Renal Data System. USRDS 2000 Annual Data Report*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2000. Available at: http://www.usrds.org/atlas_2000.htm. Accessed September 12, 2003.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1–S266.
4. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension*. 1989;13(5 suppl):I80–I93.
5. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis*. 1998;32:853–906.
6. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32:S112–S119.
7. American Heart Association. *Heart Disease and Stroke Statistics—2003 Update*. Dallas, Tex: American Heart Association; 2002. Available at: http://www.americanheart.org/presenter.jhtml?identifier=3000090. Accessed September 12, 2003.
8. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
9. Levin A, Singer J, Thompson CR, et al. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis*. 1996;27:347–354.
10. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. *Am J Med*. 1988;84:985–992.
11. Parfrey PS, Harnett JD, Foley RN, et al. Impact of renal transplantation on uremic cardiomyopathy. *Transplantation*. 1995;60:908–914.
12. Hernandez D, Lacalzada J, Rufino M, et al. Prediction of left ventricular mass changes after renal transplantation by polymorphism of the angiotensin-converting enzyme gene. *Kidney Int*. 1997;51:1205–1211.
13. Peteiro J, Alvarez N, Calviño R, et al. Changes in left ventricular mass and filling after renal transplantation are related to changes in blood pressure: an echocardiographic and pulsed Doppler study. *Cardiology*. 1994;85:273–283.
14. Huting J. Course of left ventricular hypertrophy and function in end-stage renal disease after renal transplantation. *Am J Cardiol*. 1992;70:1481–1484.
15. Himelman RB, Landzberg JS, Simonson JS, et al. Cardiac consequences of renal transplantation: changes in left ventricular morphology and function. *J Am Coll Cardiol*. 1988;12:915–923.
16. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *US Renal Data System. USRDS 1997 Annual Data Report*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1997. Available at: http://www.usrds.org/adr_1997.htm. Accessed September 15, 2003.
17. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int*. 2000;58:353–362.
18. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int*. 1995;47:186–192.
19. Warram JH, Gearin G, Laffel L, et al. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol*. 1996;7:930–937.
20. American Diabetes Association. Clinical practice recommendations 2001. *Diabetes Care*. 2001;24(suppl 1):S1–S133. [See pp S69–S72.]
21. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis*. 1999;33:1004–1010.
22. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.

23. Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol.* 2000;11:155A.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41.
25. Obrador GT, Arora P, Kausz AT, et al. Level of renal function at the initiation of dialysis in the U.S. end-stage renal disease population. *Kidney Int.* 1999;56:2227–2235.
26. Levey AS. Clinical practice: non-diabetic kidney disease. *N Engl J Med.* 2002;347:1505–1511.
27. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice: nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2002;346:1145–1151.
28. London GM, Marchais SJ, Guerin AP, et al. Arterial structure and function in end-stage renal disease. *Nephrol Dial Transplant.* 2002;17: 1713–1724.
29. Tonelli M, Bohm C, Pandeya S, et al. Cardiac risk factors and use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis.* 2001;37:484–489.
30. Jungers P, Massy ZA, Khoa TN, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. *Nephrol Dial Transplant.* 1997;12: 2597–2602.
31. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant.* 2000;15:218–223.
32. Rabbat CG, Treleaven DJ, Russell JD, et al. Prognostic value of myocardial perfusion studies in patients with end stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. *J Am Soc Nephrol.* 2003;14:431–439.
33. Rostand SG, Kirk KA, Rutsky EA. Dialysis-associated ischemic heart disease: insights from coronary angiography. *Kidney Int.* 1984;25: 653–659.
34. Mitchell GF, Izzo JL, Lacourciere Y, et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. *Circulation.* 2002;105:2955–2961.
35. Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation.* 1999;99:2434–2439.
36. Blacher J, Pannier B, Guerin AP, et al. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension.* 1998;32:570–574.
37. Guerin AP, Blacher J, Pannier B, et al. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation.* 2001;103:987–992.
38. Klassen PS, Lowrie EG, Reddan DN, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA.* 2002;287:1548–1555.
39. Harnett JD, Foley RN, Kent GM, et al. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int.* 1995;47:884–890.
40. Harnett JD, Murphy B, Collingwood P, et al. The reliability and validity of echocardiographic measurement of left ventricular mass index in hemodialysis patients. *Nephron.* 1993;65:212–214.
41. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. *Am J Kidney Dis.* 2000;35(4 suppl 1):S117–S131.
42. Anderson KM, Wilson PW, Odell PM, et al. An updated coronary risk profile: a statement for health professionals. *Circulation.* 1991;83: 356–362.
43. Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97: 1837–1847.
44. Foley RN, Parfrey PS, Harnett JD, et al. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol.* 1995;5:2024–2031.
45. Port FK, Hulbert-Shearon TE, Wolfe RA, et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis.* 1999;33:507–517.
46. Zager PG, Nikolic J, Brown RH, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int.* 1998;54:561–569. Erratum in: *Kidney Int.* 1998;54:1417.
47. Iseki K, Yamazato M, Tozawa M, et al. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int.* 2002;61:1887–1893.
48. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis.* 1990;15:458–482.
49. Foley RN, Parfrey PS, Harnett JD, et al. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int.* 1996;49:1379–1385.
50. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol.* 2002;13:1918–1927.
51. Sarnak MJ, Coronado BE, Greene T, et al. Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol.* 2002;57:327–335.
52. Uhlig K, Levey AS, Sarnak MJ. Traditional cardiac risk factors in individuals with chronic kidney disease. *Semin Dial.* 2003;16:118–127.
53. National Kidney Foundation K/DOQI clinical practice guidelines on managing dyslipidemias in chronic kidney disease. *Am J Kidney Dis.* 2003;41(suppl 3):S1–S77.
54. Boaz M, Matas Z, Biro A, et al. Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis. *Kidney Int.* 1999;56: 1078–1083.
55. Bostom AG, Shemin D, Verhouf P, et al. Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients: a prospective study. *Arterioscler Thromb Vasc Biol.* 1997;17:2554–2558.
56. Mallamaci F, Zoccali C, Tripepi G, et al. Hyperhomocysteinaemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int.* 2002;61:609–614.
57. Zimmerman J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int.* 1999;55:648–658.
58. Wahn F, Daniel V, Kronenberg F, et al. Impact of apolipoprotein(a) phenotypes on long-term renal transplant survival. *J Am Soc Nephrol.* 2001;12:1052–1058.
59. Longenecker JC, Klag MJ, Marcovina SM, et al. Small apolipoprotein(a) size predicts mortality in end-stage renal disease: the CHOICE study. *Circulation.* 2002;106:2812–2818.
60. Kronenberg F, Neyer U, Lhotta K, et al. The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. *J Am Soc Nephrol.* 1999;10:1027–1036.
61. Himmelfarb J, Stenvinkel P, Ikizler TA, et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int.* 2002;62:1524–1538.
62. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? *Kidney Int.* 2001;59:407–414.
63. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis.* 1999;34:125–134.
64. Guerin AP, London GM, Marchais SJ, et al. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant.* 2000;15:1014–1021.
65. Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorous and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis.* 1998;31:607–617.
66. Collins AJ. Influence of target hemoglobin in dialysis patients on morbidity and mortality. *Kidney Int.* 2002;61:S44–S48.
67. Yeun JY, Levine RA, Mantadilok V, et al. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis.* 2000;35:469–476.
68. Ma JZ, Ebben J, Xia H, et al. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol.* 1999;10:610–619.
69. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339: 584–590.
70. Boaz M, Smetana S, Weinstein T, et al. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial. *Lancet.* 2000;356: 1213–1218.
71. Tepel M, van der Giet M, Statz M, et al. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation.* 2003;107:992–995.
72. Yusuf S, Dagenais G, Pogue J, et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Pre-

vention Evaluation Study Investigators. *N Engl J Med.* 2000;342:154–160.
73. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after myocardial infarction among patients on long-term dialysis. *N Engl J Med.* 1998;339:799–805.
74. Donahue RP, Goldberg RJ, Chen Z, et al. The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. *J Clin Epidemiol.* 1993;46:245–252.
75. Dimeny EM. Cardiovascular disease after renal transplantation. *Kidney Int.* 2002;61:S78–S84.
76. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. *Kidney Int.* 2000;57:307–313.
77. Lindholm A, Albrechtsen D, Frodin L, et al. Ischemic heart disease—major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation.* 1995;60:451–457.
78. Kasiske BL, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol.* 2000;11:1735–1743.
79. Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med.* 2002;347:797–805.
80. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001;286:421–426.
81. Lee KU, Park JY, Kim SW, et al. Prevalence and associated features of albuminuria in Koreans with NIDDM. *Diabetes Care.* 1995;18:793–799.
82. Mykkanen L, Zaccaro DJ, O'Leary DH, et al. Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects: the insulin resistance atherosclerosis study (IRAS). *Stroke.* 1997;28:1710–1716.
83. Suzuki K, Kato K, Hanyu O, et al. Left ventricular mass index increases in proportion to the progression of diabetic nephropathy in type 2 diabetic patients. *Diabetes Res Clin Pract.* 2001;54:173–180.
84. Stephenson JM, Kenny S, Stevens LK, et al. Proteinuria and mortality in diabetes: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabet Med.* 1995;12:149–155.
85. Schleiffer T, Holken H, Brass H. Morbidity in 565 type 2 diabetic patients according to stage of nephropathy. *J Diabetes Complications.* 1998;12:103–109.
86. Howard BV, Lee ET, Cowan LD, et al. Coronary heart disease prevalence and its relation to risk factors in American Indians: the Strong Heart study. *Am J Epidemiol.* 1995;142:254–268.
87. John L, Rao PS, Kanagasabapathy AS. Prevalence of diabetic nephropathy in non-insulin dependent diabetics. *Indian J Med Res.* 1991;94:24–29.
88. Agewall S, Wikstrand J, Ljungman S, et al. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol.* 1997;80:164–169.
89. Gall MA, Borch-Johnsen K, Hougaard P, et al. Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes.* 1995;44:1303–1309.
90. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non–insulin-dependent diabetes mellitus: a systematic overview of the literature. *Arch Intern Med.* 1997;157:1413–1418.
91. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med.* 1984;310:356–360.
92. Messent JW, Elliott TG, Hill RD, et al. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. *Kidney Int.* 1992;41:836–839.
93. Mattinen H, Haffner SM, Lehto S, et al. Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non–insulin-dependent diabetic subjects. *Stroke.* 1996;27:2033–2039.
94. Rossing P, Hougaard P, Borch-Johnsen K, et al. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ.* 1996;313:779–784.
95. Stehouwer CD, Gall MA, Twisk JW, et al. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes.* 2002;51:1157–1165.
96. Uusitupa MI, Niskanen LK, Siitonen O, et al. Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 diabetic and non-diabetic subjects. *Diabetologia.* 1993;36:1175–1184.
97. Valmadrid CT, Klein R, Moss SE, et al. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med.* 2000;160:1093–1100.
98. Stehouwer CD, Nauta JJ, Zeldenrust GC, et al. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin dependent diabetes mellitus. *Lancet.* 1992;340:319–323.
99. Stehouwer CD, Lambert J, Donker AJ, et al. Endothelial dysfunction and pathogenesis of diabetic angiopathy. *Cardiovasc Res.* 1997;34:55–68.
100. Festa A, D'Agostino R, Howard G, et al. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: the insulin resistance atherosclerosis study. *Kidney Int.* 2000;58:1703–1710.
101. Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med.* 1998;338:1202–1211.
102. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis.* 1998;32(5 suppl 3):S142–S156.
103. Pontremoli R, Sofia A, Ravera M, et al. Prevalence and clinical correlates of microalbuminuria in essential hypertension: the MAGIC study. Microalbuminuria: a Genoa Investigation on Complications. *Hypertension.* 1997;30:1135–1143.
104. Dell'Omo G, Penno G, Giorgi D, et al. Association between high-normal albuminuria and risk factors for cardiovascular and renal disease in essential hypertensive men. *Am J Kidney Dis.* 2002;40:1–8.
105. Hillege HL, Janssen WM, Bak AA, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med.* 2001;249:519–526.
106. Bigazzi R, Bianchi S, Nenci R, et al. Increased thickness of the carotid artery in patients with essential hypertension and microalbuminuria. *J Hum Hypertens.* 1995;9:827–833.
107. Wachtell K, Palmieri V, Olsen MH, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Losartan Intervention for Endpoint Reduction. *Am Heart J.* 2002;143:319–326.
108. Wachtell K, Olsen MH, Dahlof B, et al. Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. *J Hypertens.* 2002;20:405–412.
109. Diercks GF, Hillege HL, van Boven A, et al. Relation between albumin in the urine and electrocardiographic markers of myocardial ischemia in patients without diabetes mellitus. *Am J Cardiol.* 2001;88:771–774.
110. Culleton BF, Larson MG, Parfrey PS, et al. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med.* 2000;109:1–8.
111. De Leeuw PW, Thijs L, Birkenhager WH, et al. Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from the Syst-Eur trial. *J Am Soc Nephrol.* 2002;13:2213–2222.
112. Diercks GF, Hillege HL, van Boven AJ, et al. Microalbuminuria modifies the mortality risk associated with electrocardiographic ST-T segment changes. *J Am Coll Cardiol.* 2002;40:1401–1407.
113. Damsgaard EM, Froland A, Jorgensen OD, et al. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ.* 1990;300:297–300.
114. Grimm RJ, Svendsen K, Kasiske B, et al. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group; Multiple Risk Factor Intervention Trial. *Kidney Int.* 1997;62:S10–S14.
115. Ljungman S, Wikstrand J, Hartford M, et al. Urinary albumin excretion—a predictor of risk of cardiovascular disease: a prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens.* 1996;9:770–778.
116. Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation.* 2002;106:1777–1782.
117. Jager A, Kostense PJ, Ruhe HG, et al. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol.* 1999;19:617–624.
118. Kannel WB, Stampfer MJ, Castelli WP, et al. The prognostic significance of proteinuria: the Framingham study. *Am Heart J.* 1984;108:1347–1352.
119. Muntner P, He J, Hamm L, et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol.* 2002;13:745–753.

120. Kuusisto J, Mykkanen L, Pyorala K, et al. Hyperinsulinemic microalbuminuria: a new risk indicator for coronary heart disease. *Circulation*. 1995;91:831–837.
121. Roest M, Banga JD, Janssen WM, et al. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. *Circulation*. 2001;103:3057–3061.
122. Ordonez JD, Hiatt RA, Killebrew EJ, et al. The increased risk of coronary artery disease associated with nephrotic syndrome. *Kidney Int*. 1993;44:638–642.
123. Wagner DK, Harris T, Madans JH. Proteinuria as a biomarker: risk of subsequent morbidity and mortality. *Environ Res*. 1994;66:160–172.
124. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects: Islington diabetes survey. *Lancet*. 1988;2(8610):530–533.
125. Pedrinelli R, Dell'Omo G, Penno G, et al. Non-diabetic microalbuminuria, endothelial dysfunction and cardiovascular disease. *Vasc Med*. 2001;6:257–264.
126. Gosling P. Microalbuminuria: a marker of systemic disease. *Br J Hosp Med*. 1995;54:285–290.
127. Clausen P, Feldt-Rasmussen B, Jensen G, et al. Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: a 4-year prospective study. *Clin Sci*. 1999;97:37–43.
128. Jensen JS. Renal and systemic transvascular albumin leakage in severe atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1995;15:1324–1329.
129. Clausen P, Jensen JS, Jensen G, et al. Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation*. 2001;103:1869–1874.
130. Paisley KE, Beaman M, Tooke JE, et al. Endothelial dysfunction and inflammation in asymptomatic proteinuria. *Kidney Int*. 2003;63:624–633.
131. Culleton BF, Larson MG, Wilson PW, et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int*. 1999;56:2214–2219.
132. Mann JF, Gerstein HC, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med*. 2001;134:629–636.
133. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular disease in the community. *J Am Coll Cardiol*. 2003;41:47–55.
134. Ruilope LM, Salvetti A, Jamerson K, et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol*. 2001;12:218–225.
135. Shlipak MG, Fried LF, Crump C, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int*. 2002;62:997–1004.
136. Reis SE, Olson MB, Fried L, et al. Mild renal insufficiency is associated with angiographic coronary artery disease in women. *Circulation*. 2002;105:2826–2829.
137. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int*. 2003;63:1121–1129.
138. Friedman PJ. Serum creatinine: an independent predictor of survival after stroke. *J Intern Med*. 1991;229:175–179.
139. McCullough PA, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. *J Am Coll Cardiol*. 2000;36:679–684.
140. McCullough PA, Nowak RM, Foreback C, et al. Emergency evaluation of chest pain in patients with advanced kidney disease. *Arch Intern Med*. 2002;162:2464–2468.
141. Soman SS, Sandberg KR, Bozzak S, et al. The independent association of renal dysfunction and arrhythmias in critically ill patients. *Chest*. 2002;122:669–677.
142. Matts JP, Karnegis JN, Campos CT, et al. Serum creatinine as an independent predictor of coronary heart disease mortality in normotensive survivors of myocardial infarction. *J Fam Pract*. 1993;36:497–503.
143. Walsh CR, O'Donnell CJ, Camargo CA, et al. Elevated serum creatinine is associated with 1-year mortality after myocardial infarction. *Am Heart J*. 2002;144:1003–1011.
144. Rubenstein MH, Harrell LC, Sheynberg BV, et al. Are patients with renal failure good candidates for percutaneous coronary revascularization in the new device era. *Circulation*. 2000;102:2966–2972.
145. Hemmelgarn BR, Ghali WA, Quan H, et al. Poor long-term survival after coronary angiography in patients with renal insufficiency. *Am J Kidney Dis*. 2001;37:64–72.
146. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*. 2001;37:1191–1200. Erratum in: *Am J Kidney Dis*. 2001;38:701.
147. Shlipak MG, Simon JA, Grady D, et al. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol*. 2001;38:705–711.
148. Shlipak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med*. 2002;137:555–562.
149. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:681–689.
150. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol*. 2002;40:1801–1808.
151. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation*. 2000;102:203–210.
152. McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol*. 2002;13:1928–1936.
153. Mahon NG, Blackstone EH, Francis GS, et al. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol*. 2002;40:1106–1113.
154. Szczech LA, Reddan DN, Owen WF, et al. Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int*. 2001;60:292–299.
155. Szczech LA, Best PJ, Crowley E, et al. Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. *Circulation*. 2002;105:2253–2258.
156. Gruberg L, Weissman NJ, Waksman R, et al. Comparison of outcomes after percutaneous coronary revascularization with stents in patients with and without mild chronic renal insufficiency. *Am J Cardiol*. 2002;89:54–57.
157. Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation*. 2002;106:974–980.
158. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2002;39:1113–1119.
159. Beddhu S, Allen-Brady K, Cheung AK, et al. Impact of renal failure on the risk of myocardial infarction and death. *Kidney Int*. 2002;62:1776–1783.
160. Januzzi JL, Snapinn SM, DiBattiste PM, et al. Benefits and safety of tirofiban among acute coronary syndrome patients with mild to moderate renal insufficiency: results from the platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms (PRISM-PLUS) trial. *Circulation*. 2002;105:2361–2366.
161. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med*. 2002;137:563–570.
162. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA*. 1998;279:585–592.
163. Manolio TA, Kronmal RA, Burke GL, et al. Short-term predictors of incident stroke in older adults: the Cardiovascular Health Study. *Stroke*. 1996;27:1479–1486.
164. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2000;35:1628–1637.
165. Henry RM, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn study. *Kidney Int*. 2002;62:1402–1407.
166. Schillaci G, Reboldi G, Verdecchia P. High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med*. 2001;161:886–891.

167. Flack JM, Neaton JD, Daniels B, et al. Ethnicity and renal disease: lessons from the multiple risk factor intervention trial and the treatment of mild hypertension study. *Am J Kidney Dis*. 1993;21(4 supp 1):31–40.
168. Shaw RE, Anderson HV, Brindis RO, et al. Development of a risk adjustment mortality model using the American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) experience: 1998–2000. *J Am Coll Cardiol*. 2002;39:1104–1112.
169. O'Brien MM, Gonzales R, Shroyer AL, et al. Modest serum creatinine elevation affects adverse outcome after general surgery. *Kidney Int*. 2002;62:585–592.
170. Garg AX, Clark WF, Haynes RB, et al. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int*. 2002;61:1486–1494.
171. Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke*. 1997;28:557–563.
172. Gruberg L, Weissman NJ, Pichard AD, et al. Impact of renal function on morbidity and mortality after percutaneous aortocoronary saphenous vein graft intervention. *Am Heart J*. 2003;145:529–534.
173. Freeman RV, Mehta RH, Al Badr W, et al. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol*. 2003;41:718–724.
174. Wilson S, Foo K, Cunningham J, et al. Renal function and risk stratification in acute coronary syndromes. *Am J Cardiol*. 2003;91:1051–1054.
175. Anderson RJ, O'Brien M, MaWhinney S, et al. Mild renal failure is associated with adverse outcome after cardiac valve surgery. *Am J Kidney Dis*. 2000;35:1127–1134.
176. Anderson RJ, O'Brien M, MaWhinney S, et al. Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery: VA Cooperative Study #5. *Kidney Int*. 1999;55:1057–1062.
177. Reinecke H, Trey T, Matzkies F, et al. Grade of chronic renal failure, and acute and long term outcome after percutaneous coronary interventions. *Kidney Int*. 2003;63:696–701.
178. Rubenstein MH, Sheynberg BV, Harrell LC, et al. Effectiveness of and adverse events after percutaneous coronary intervention in patients with mild versus severe renal failure. *Am J Cardiol*. 2001;87:856–860.
179. Reddan DN, Szczech LA. Renal insufficiency and the risk of cardiovascular mortality. *Kidney Int*. 2002;62:1474–1475.
180. Arnadottir M, Hultberg B, Nilsson-Ehle P, et al. The effect of reduced glomerular filtration rate on plasma total homocysteine concentration. *Scand J Clin Lab Invest*. 1996;56:41–46.
181. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation*. 2003;107:87–92.
182. McCullough PA, Sandberg KR, Borzak S, et al. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J*. 2002;144:226–232.
183. Reddan DN, O'Shea JC, Sarembock IJ, et al. Treatment effects of eptifibatide in planned coronary stent implantation in patients with chronic kidney disease (ESPRIT trial). *Am J Cardiol*. 2003;91:17–21.
184. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368–375.
185. Rigatto C, Parfrey P, Foley R, et al. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol*. 2002;13:1084–1090.
186. Chobanian AV, Bakris GL, Black HR, et al: National Heart, Lung and Blood Institute Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
187. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.

KEY WORDS: AHA Scientific Statements ■ kidney ■ cardiovascular diseases ■ risk factors

Exhibit 2

Nephrol Dial Transplant (2000) 15 [Suppl 3]: 8–13

Nephrology Dialysis Transplantation

Consequences of late referral on patient outcomes

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Abstract There is growing awareness of a need not only to identify patients with chronic renal failure (CRF) at an earlier stage in the disease process, but also to initiate treatment strategies earlier, in order to delay both progression of CRF and co-morbid diseases and to define the optimal time required to prepare CRF patients for renal replacement therapy (RRT). These three strategies are linked, and rely on appropriate identification of patients at risk of renal disease. The challenge currently facing nephrologists is both how to minimize the consequences of late referral and how to improve the timeliness of referral.

Published studies support the notion that outcomes are poor in patients who access specialized nephrology care late in the course of their renal disease (just prior to the need for dialysis). A National Institute of Health consensus publication recommends early referral to a multidisciplinary renal care team, and the recent Canadian Society of Nephrology guidelines recommend that at least 12 months are needed prior to initiation of dialysis for adequate medical and psychological preparation for RRT. Despite these recommendations, a substantial proportion (20–50%) of patients starts dialysis without prior exposure to nephrologists.

Limited data exist on current referral patterns to nephrologists. Diabetes and/or hypertension cause renal disease in up to 40% of patients requiring dialysis. These patients are presumably being monitored by internists, endocrinologists or cardiologists, and many referrals come from these physicians; other patients may be referred by general practitioners.

Data regarding disease status at the time of referral are also limited. Substantial cardiovascular disease and risk factors are evident at the time of referral. Most of the literature describes data for those starting dialysis (i.e. late referral) rather than a broader spectrum of all patients with renal insufficiency referred to nephrologists. Reasons for late referral include insensitivity of current screening tools. Serum creatinine is well known to be an inaccurate marker of renal dysfunction, and too insensitive to identify patients with *very* early stages of disease, thus contributing to the prevalence of late referrals. Physician and patient attitudes are other barriers to early referral and need to be studied more fully.

The consequences of late referrals include increased morbidity, mortality, and resource utilization. There is also an impact on patients' quality of life and missed opportunities for pre-emptive transplantation. Late referral also limits therapeutic options, and these limitations have consequences on long-term outcomes once patients are on dialysis.

It is clear that late referral of patients with CRF obviates the opportunity for significant delay of disease progression and institution of proactive strategies to reduce the overall burden of illness in the population. There is ample evidence that strategies to delay progression of renal disease are effective, as are strategies to reduce cardiovascular disease. Anaemia and a fall in haemoglobin concentration have been associated with left ventricular hypertrophy and with growth of the left ventricle. A combined approach is necessary for best nephrological clinical practice, with a clear definition of early renal insufficiency; this will involve the development of tools to permit early identification of patients with early renal insufficiency, and the implementation of strategies to optimize treatments aimed at both delaying progression and preparing patients for RRT.

Key words: dialysis; early renal insufficiency; renal disease; screening; serum creatinine

Introduction

Morbidity and mortality remain high among patients on dialysis, despite advances in technology and improved understanding of treatment strategies. Factors that are present at the initiation of dialysis, as well as those that exist before its commencement, have an impact on patient outcomes. If long-term patient outcomes are to be improved, then there is a need for earlier identification of, and intervention in, patients with renal disease. Strategies have been described that delay the progression of both renal and comorbid diseases. Optimal treatment of patients before initiation

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of dialysis is contingent on an accurate definition of the population categorized as 'pre-dialysis' patients. However, the term 'pre-dialysis' is still used to define a heterogeneous group of patients, including those who are referred both 'early' and 'late' in the clinical course of their renal disease. Once accurate definitions and terminology are established, it will be important to determine the barriers to timely referral so that they can be systematically addressed. Finally, it is important to establish goals for the treatment of patients with chronic or progressive renal failure, and strategies by which to achieve those goals. This paper addresses issues related to late referral to nephrologists, focusing on current referral patterns and their consequences, the current burden of illness in the renal population, both prior to and at initiation of dialysis, and the known consequences of late referral.

Current referral patterns

Current referral patterns can be classified into three major categories: early, late, and not referred (Figure 1). For patients with renal insufficiency, the consequence of never being referred to a nephrologist is death; the extent to which this currently occurs is not known. Alternatively, if patients are referred early in the course of their renal disease, opportunities to intervene exist that may delay or halt the progression of the renal disease process and/or of associated cardiovascular, metabolic and bone diseases [1–4]. Furthermore, with early referral, adequate physical, social, and psychological preparation for renal replacement therapy (dialysis or transplantation) is possible. If patients are referred late in the course of their renal disease, opportunities for proactive intervention are lost, as is adequate time to prepare for arteriovenous access or living donor transplantation. Optimal therapy for patients with renal disease, therefore, includes timely referral to a nephrology team.

'Timely referral', however, remains a poorly defined term. The National Institute of Health (NIH) Consensus Conference Statement, published in 1994 [5], described the need to refer patients to a nephrology team at least 4 months before initiation of dialysis. In a 1999 Canadian Society of Nephrology publication 'timely referral' is defined as being at least 12 months prior to dialysis initiation [6]. Both definitions of timeliness presuppose that general practitioners, internists, and other specialists are able to predict when dialysis will be necessary in any given patient—a difficult skill even for trained nephrologists. Problems therefore will be encountered in defining timeliness, as a knowledge of future events is required. It has been suggested that timely referral to a nephrologist should apply to any patient who has evidence of renal impairment, or to those within high-risk groups (e.g., patients with hypertension, diabetes, or cardiovascular disease) who have abnormalities of renal function or urine sediment. For the purposes of this article, however, 'late referral' is defined as those persons commencing dialysis therapy within 4 months of being known to a nephrologist.

It is estimated that 20–50% of patients starting dialysis are late referrals [7]. The variation in reported prevalence rates is explained by differences in defining the group of patients for whom there was an opportunity for earlier referral. Approximately 20–25% of patients starting dialysis were previously known to a physician, but were not referred to a nephrologist in a 'timely' manner. The other 25% of patients classified as 'referred late' were not referred earlier for a number of reasons: the patients either had acute renal failure that did not resolve, or rapidly progressive glomerulonephritis, or were non-compliant or asymptomatic, or were unknown to a physician.

Magnitude of the problem of renal insufficiency

To view the current problem of late referral in context, it is useful to review population data that define patients at risk, or patients who have early renal disease. Data from the National Health and Nutrition

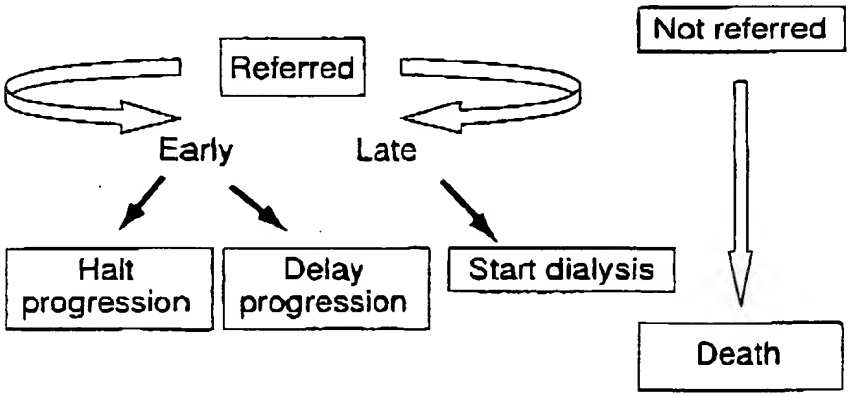

Fig. 1. Referral patterns for patients with renal insufficiency.

Examination Survey (NHANES III) of 12000 people in the United States has estimated the prevalence of early renal insufficiency (ERI) to be between 10.9 million and 0.8 million, depending on the definition of 'early' renal disease (i.e. serum creatinine concentrations >1.5 g/dl or >2.0 g/dl) [8]. In the UK, Khan *et al.* [9] estimated the annual incidence in the population of serum creatinine concentrations greater than 300 μmol/l to be approximately 600 per million population. If individuals over the age of 85 years and individuals with malignancy are excluded, the incidence of serum creatinine is still impressive at approximately 450 per million [9]. The proportion of the population, therefore, who ought to be referred to a nephrologist is huge and potentially beyond the current capabilities of most national nephrology communities. If prevention or delay of renal disease progression does lead to improved patient outcomes, then planning for increased workload and strategies is essential.

Screening for renal disease

Interestingly, the estimates of populations who potentially require renal replacement services are based on defining renal dysfunction according to serum creatinine concentrations, unadjusted for body size or gender. The true prevalence of individuals with impaired renal function is likely to be much higher if renal function, not just serum creatinine concentration, is used to define renal dysfunction. The recent Modification of Diet in Renal Disease (MDRD) formula, and older formulae, such as Cockcroft–Gault, have been used to improve estimates of renal function from simple laboratory parameters [10,11]. In a large urban population, Duncan *et al.* [12] recently surveyed all patients attending a centralized municipal set of laboratories and applied the conservative, simple Cockcroft–Gault formula to all patients whose serum creatinine was measured. Using a creatinine clearance cut-off of less than 50% to define abnormal, it was demonstrated that of 15% those patients with normal serum creatinine concentrations according to laboratory criteria had abnormal renal function when the Cockcroft–Gault formula was applied. These results identified a group of patients who were at risk but were not easily identified by non-nephrologists. Recently, Couchoud and colleagues [13] proposed that a set of sex- and age-corrected serum creatinine cut-off concentrations should be implemented to appreciate differences in renal function not reflected by serum creatinine. The first step in ensuring timely referral of patients to nephrologists is the implementation of sensitive screening tools.

In a recent editorial in this journal, Jungers [14] addressed the utility and feasibility of screening for renal insufficiency. He concluded that since the 'principles of preventative therapy are now well established, and the evidence that appropriate drug intervention is effective in halting or at least slowing renal insufficiency', strategies to improve early identification and care of renal patients are essential [14]. However, current patterns of 'late referral' may reflect, at least in part, difficulties with today's screening tools. Strategies that serve to educate both patients and physicians about the meaning of specific tests of renal function may be useful. Examples of similar campaigns to educate patients and physicians can be found in the field of cardiovascular disease, with respect to cholesterol screening [15,16].

At present, nephrologists should focus on those renal patients who are known to the medical system but who have not yet been referred to the kidney disease specialist. Reasons for non-referral to nephrologists, therefore, need to be examined. These reasons include non-recognition of ERI (see above), and non-nephrologist attitudes towards (i) the utility of dialysis, (ii) the role of nephrologists, and (iii), in some health care systems or cases, physician concerns about loss of income. It is beyond the scope of this paper to review each of these in depth, but it is important to acknowledge that the problems of non-referral and delayed or late referral are related both to issues of identification of renal dysfunction and to attitudes towards referral.

Physician factors

Attitudes towards referral by non-nephrologists have been studied by only a few investigators. Mendelssohn *et al.* [17] demonstrated that 84.3% of general practitioners in Ontario, Canada, would not refer patients with serum creatinine concentrations between 120 and 150 μmol/l (which reflects at least 50% loss of renal function), and that almost 30% would not even refer patients with serum creatinine concentrations of 151–300 μmol/l. Similar attitudes have been documented in other countries including the USA, the UK, and France.

Other reasons for delayed referral include the perceived futility of dialysis for older, diabetic patients and the perceived non-utility of nephrology care prior to the actual start of dialysis. Specifically, many specialists perceive nephrologists only as providers of dialysis therapy. A problem of delayed referral even at low levels of renal dysfunction may be due to a lack of appreciation of the meaning of serum creatinine concentrations in relation to renal function, or a lack of appreciation of the utility of nephrological care during early stages of renal insufficiency. Ultimately, late referral translates into lost opportunities for intervention, and therefore contributes to the poor outcomes seen in patients who are 'referred late'. Interestingly, there is a dearth of publications in general medical journals describing the impact of nephrology care on patient outcomes. The few studies that have specifically addressed nephrological care and patient outcomes have been published in nephrology journals [1,18–22].

Consequences of delayed referral

The consequences of late referral have been well documented by numerous investigators since as early as 1972 [11,23–27]. Morbidity and mortality among patients 'referred late' is worse than among those referred in a timely manner. The cost to the health care system in terms of hospitalizations and procedures is also higher.

Numerous clinical, haematological, hormonal and metabolic abnormalities have been documented in patients at the time of dialysis initiation, including anaemia, malnutrition, hyperparathyroidism, hyperphosphataemia, hypocalcaemia, acidaemia, hypertension, and congestive heart failure. The presence of low albumin, anaemia, left ventricular hypertrophy (LVH), and congestive heart failure at dialysis initiation have been linked to poor dialysis outcomes [28–31]. Each of these parameters is potentially modifiable. Although no data exist yet to link changes in these factors to changes in patient outcomes, it would seem rational that attention to these abnormalities before dialysis initiation would have a positive impact on longer-term patient outcomes. However, large prospective studies are needed to confirm such a positive impact on patient outcomes.

A very direct consequence of later referral is the lack of permanent vascular access, and the precipitous commencement of dialysis in unstable patients. Studies have shown that late referral leads to an increase in infection, morbidity, and even mortality [19,21,32]. Furthermore, modality selection may be influenced by the timing of referral: those patients who are referred to nephrology teams early in the course of their disease are more likely to choose peritoneal dialysis rather than haemodialysis [33,34]. Delayed referral therefore has major direct consequences for patients and for health care systems.

Publications to date have described the status of patients at the time of dialysis initiation relative to the time of referral. Problems with these analyses include the retrospective nature of the studies, the lack of reasons given for early *vs* late referral, and non-uniform definitions of 'early' *vs* 'late' referral. Despite these shortcomings, the data are remarkably similar irrespective of the country or health care system from which they are derived. Patients who are referred to a nephrologist early (usually defined as more than 4 months prior to beginning of renal replacement therapy) are younger, and have higher albumin, bicarbonate, and haemoglobin concentrations than those who are referred late; in addition, patients referred early are more likely to have a permanent access and to have chosen peritoneal dialysis as an initial modality. Many of the publications pre-date the NIH Consensus guideline recommendations. Curtis *et al.* therefore examined current practice in a recent Canadian survey [manuscript in preparation]. Table 1 shows that similar referral patterns are evident, even in the current era (1998–1999). Approximately 30% of patients commencing dialysis in Canada were known to nephrologists for less than 3 months prior to starting dialysis; these patients were older, more likely to have diabetes, had started haemodialysis through a temporary line, and had lower albumin and haemoglobin concentrations at the initiation of dialysis.

Table 1. Patterns of referral to a nephrologist (recent Canadian survey: 15 centres/7 provinces: 1-month sample)

	All (238)	Known (157)	Not known (84)	p-value
Age (years)	59	57	62.5	0.01
Diabetes (%)	38	35	36	0.54
HD (%)	67	68	65	0.64
Temp. line (%)	52.5	41	75	0.001
Albumin (g/l)	31	33	29*	0.002
Hb (g/dl)	9.2	9.4	8.9	0.051
CCr	10.9	11	10.8	0.057

*Significant difference.

There is substantial evidence to show that late referral of patients to nephrologists results in poorer clinical status at the time of dialysis initiation. Given that the factors known to adversely affect long-term dialysis outcomes are present in late-referred patients, a proportion of the morbidity and mortality of patients on dialysis may therefore be attributed to the failure to refer patients to a nephrologist and institute appropriate treatments in a timely manner prior to dialysis initiation.

Data available from the Canadian Multicentre Cohort Study of Patients with Early Renal Insufficiency (funded by the Kidney Foundation of Canada) allows some documentation as to the status of patients seen by nephrologists. A total of 446 patients seen by nephrologists in eight centres across Canada were entered. The mean creatinine clearance of the group was 36 ml/min (mean serum creatinine concentration of 263 μmol/l), indicating substantial, although not end-stage, renal impairment. Interestingly, almost 25% of the group had a creatinine clearance of less than 25% [35]. At study entry, this group of patients demonstrated a high prevalence of cardiovascular diseases and risk factors for cardiovascular disease. Specifically, the prevalence of LVH was 36% overall, and 48% in the group with a calculated creatinine clearance of less than 25 ml/min (i.e. the group most likely to commence dialysis). In this population, as in the dialysis population, anaemia and a fall in haemoglobin concentration were associated with LVH and with growth of the left ventricle. Cardiac symptoms, according to New York Heart Association and Canadian Cardiovascular Society classifications, as well as hospitalizations, are associated with lower haemoglobin concentrations, lower renal function values, faster rates of renal decline, and growth of the left ventricle. In identifying modifiable risk factors, this study highlighted the opportunities for intervention that exist in the renal population prior to dialysis.

Obrador *et al.* [36] reported that even in those

patients seen by nephrologists, sub-optimal care is being delivered. Their recent study reviewed patients seen in different nephrology settings over a 2-year period; their data show that almost 60% of patients seen by nephrologists commence dialysis with albumin concentrations below 35 g/l, and that only 25% of anaemic patients receive epoetin. Patients who were older, female, Caucasian, and had private medical insurance were more likely to receive epoetin [36]. These findings demonstrate that care may not be optimal even in current nephrology practice. As nephrologists attempting to increase the numbers of patients referred earlier in the course of disease, it is important that improved outcomes at both dialysis initiation and in the long term are demonstrated by further studies. Levin *et al.* [19] have previously established that when patients attend a multidisciplinary clinic, the patient's clinical status is improved at dialysis initiation and over the first 6 months of dialysis. However, the optimal timing and the extent and type of interventions necessary to improve renal patient outcomes still need to be defined.

Conclusion

The consequences of late referral to nephrologists on patient outcomes are profound and far reaching. Effective strategies currently exist to prevent or delay both the progression of renal disease and the serious co-morbidities that exist in the population with renal insufficiency. The most serious consequence of late referral to a nephrologist is that it is too late to apply these known strategies to patients who may have benefited had they been referred earlier. Equally serious is the inability to study systematically the impact of different strategies in patients with chronic renal insufficiency. As a result, clinicians and researchers are unable to reduce the burden of illness in the renal patient population, and the subsequent impact of that burden of illness on health care systems. Obvious strategies to improve this situation include clearly defining chronic renal insufficiency populations for both nephrologists and non-nephrologists, identifying better tools for screening, screening of high-risk populations, and educating both patients and physicians as to the utility of screening and early implementation of treatment strategies, such as preventing a fall in haemoglobin concentration. The implications of implementing these strategies and improving patient outcomes are obvious; however, both human and fiscal resources will be required.

References

1. Hood S, Sondheimer J. Impact of pre-ESRD management on dialysis outcomes: a review. *Semin Dial* 1998; 11: 175–180
2. Klahr S, Levey AS, Beck GJ *et al.* The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J. Med.* 1994; 330: 877–884
3. Modification of Diet in Renal Disease Study Group (prepared by Kopple JD *et al.*). Nutritional status of patients with different levels of chronic renal failure. *Kidney Int* 1989; 36 [Suppl 27]: 184–194
4. Fournier A, Aparicio M. Recommendations for clinical practice concerning the prevention of renal osteodystrophy before extra-renal purification. *Nephrologie* 1998; 19: 129–130
5. Morbidity and mortality of renal dialysis. NIH Consensus Statement. *Ann Intern Med* 1994; 121: 62–70
6. Mendelssohn D, Barrett B, Brownscombe L *et al.* Elevated levels of serum creatinine: recommendations for management and referral. *Can Med Assoc J* 1999; 161: 413–417
7. Arora P, Obrador GT, Ruthazer R *et al.* Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999; 10: 1281–1286
8. Jones CA, McQuillan GM, Kusek JW *et al.* Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 1998; 32: 992–999
9. Khan IH, Catto GRD, Edward N, Macleod AM. Chronic renal failure: factors influencing nephrology referral. *QJM* 1994; 87: 559–564
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999; 130: 461–470
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41
12. Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease with serum creatinine: who are we missing? *J Am Soc Nephrol* 1998; 9: 153A
13. Couchoud C, Pozet N, Labeeuw M, Pouteil-Noble C. Screening early renal failure: cut-off values for serum creatinine as an indicator of renal impairment. *Kidney Int* 1999; 55: 1878–1884
14. Jungers P. Screening for renal insufficiency: is it worthwhile? Is it feasible? *Nephrol Dial Transplant* 1999; 14: 2082–2084
15. Summary of the second report of the National Cholesterol Educational Program (NCEP). Expert panel on detection evaluation and treatment of high blood cholesterol in adults. *J Am Med Assoc* 1993; 269: 3015–3023
16. Harris DE, Record NB, Gipson GW, Pearson TA. Lipid lowering in a multidisciplinary clinic compared with primary physician management. *Am J Cardiol* 1998; 81: 929–933
17. Mendelssohn DC, Kua BT, Singer PA. Referral for dialysis in Ontario. *Arch Intern Med.* 1995; 155: 2473–2478
18. Ifudu O, Dawood M, Homel P, Friedman EA. Excess morbidity in patients starting uremia therapy without prior care by a nephrologist. *Am J Kidney Dis* 1996; 28: 841–845
19. Levin A, Lewis M, Mortiboy P *et al.* Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *Am J Kidney Dis* 1997; 29: 533–540
20. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis* 1998; 1: 398–417
21. Innes A, Rowe PA, Burden RP, Morgan AG. Early deaths on renal replacement therapy: the need for early nephrological referral. *Nephrol Dial Transplant* 1992; 7: 467–471.
22. Ismail N, Neyra R, Hakim R. The medical and economical advantages of early referral of chronic renal failure patients to renal specialists [editorial]. *Nephrol Dial Transplant* 1998; 13: 246–250
23. Bonomini V, Baldrati L, Stefoni S. Comparative cost/benefit analysis in early and late dialysis. *Nephron* 1983; 33: 1–4
24. Eadington DW, Craig KJ, Winney RJ. Comorbidity and biochemical indices modulate the impact of late referral on survival on RRT (abstract). *Nephrol Dial Transplant* 1994; 9: 960
25. Ratcliffe PJ, Phillips RE, Oliver DO. Late referral for maintenance dialysis. *BMJ* 1984; 288: 441–443
26. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G. Early referral and its impact on emergent first dialyses, health care costs, and outcome. *Am J Kidney Dis* 1998; 32: 278–283
27. Sesso R, Belasco AG. Late diagnosis of chronic renal failure and mortality on maintenance dialysis. *Nephrol Dial Transplant* 1996; 11: 2417–2420

28. Hakim R, Levin N. Malnutrition in hemodialysis patients. *Am J Kidney Dis* 1993; 21: 125–137
29. Lowrie EG, Huang WH, Lew NL. Death risk predictors among peritoneal dialysis and hemodialysis patients: a preliminary comparison. *Am J Kidney Dis* 1995; 26: 220–228
30. Madore F, Lowrie EG, Brugnara C *et al.* Anemia in hemodialysis patients: variables affecting this outcome predictor. *J Am Soc Nephrol* 1997; 8: 1921–1929
31. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; 47: 186–192
32. Jungers P, Zingraff J, Page B, Albouze G, Hannedouche T, Man NK. Detrimental effects of late referral in patients with chronic renal failure: a case control study. *Kidney Int* 1993; 41 [Suppl]: S170–173
33. Nissenson A, Prichard S, Cheng I. Non-medical factors that impact on ESRD modality selection. *Kidney Int* 1993; 40 [Suppl]: S120–127
34. Lameire N, Van Biesen W, Dombros N *et al.* The referral pattern of patients with ESRD is a determinant in the choice of dialysis modality. *Perit Dial Int* 1997; 17 [Suppl 2]: S161–166
35. Levin A, Thompson C, Ethier J, *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125–134
36. Obrador GT, Ruthazer R, Arora P, Kausz A, Pereira JB. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol* 1999; 10: 1793–1800

Exhibit C

Perspectives in Diabetes

The Need for Early Predictors of Diabetic Nephropathy Risk

Is Albumin Excretion Rate Sufficient?

M. Luiza Caramori, Paola Fioretto, and Michael Mauer

Initial studies showing an ~80% rate of progression from microalbuminuria (MA) to proteinuria in type 1 diabetic patients led to the broad acceptance of MA as a useful clinical predictor of increased diabetic nephropathy (DN) risk. Some MA patients, however, have quite advanced renal structural changes, and MA may, in these cases, be a marker rather than a predictor of DN. More recent studies have observed only about a 30–45% risk of progression of MA to proteinuria over 10 years, while about 30% of type 1 diabetic patients with MA became normoalbuminuric and the rest remained microalbuminuric. The finding that some MA patients have only mild diabetic renal lesions is consistent with the lower than originally estimated risk of progression from MA to proteinuria and with the notion that some MA patients revert to normoalbuminuria. To increase the complexity of the scenario, some normoalbuminuric long-standing type 1 diabetic patients have well-established DN lesions and ~40% of all patients destined to progress to proteinuria are normoalbuminuric at initial screening, despite many years of diabetes. A similar picture is emerging in type 2 diabetic patients, although fewer studies have been conducted. Thus, the predictive precision for MA to progress to overt nephropathy over the subsequent decade or so is considerably less than originally described. It is unclear whether this is due to changes in the natural history of DN resulting from improved glycemia and blood pressure control, or whether there were overestimates of risk in the original studies due to the small sample sizes, post hoc analyses, and variable MA definitions. Albumin excretion rate (AER) remains the best available noninvasive predictor of DN risk and should be regularly measured according to established guidelines. However, AER may be unable to define patients who are safe from or at risk of DN with an accuracy that is adequate for optimal clinical decision making or for the design of certain clinical trials. Investigations into new risk markers or into the combined use of several currently available predictive parameters are needed. *Diabetes* 49:1399–1408, 2000

The proportion of patients with end-stage renal disease (ESRD) caused by diabetes has progressively increased during the last few decades, and diabetic nephropathy (DN) is now the single most common cause of ESRD in the Western world. In fact, in 1997, 44% of all new cases of ESRD in the U.S. were diagnosed in diabetic patients, >80% of whom have type 2 diabetes (1). Although a recent study from Sweden (2) in which patients were maintained under strict glycemic control reported a decrease in the incidence of DN in type 1 diabetic patients, this result has not been confirmed (3).

Based on studies in type 1 diabetes, it had been generally considered that once overt DN, manifesting as persistent proteinuria, is present, it was only possible to slow, but not halt, the progression toward ESRD (4–6). This led investigators during the early 1980s to search for early predictors of DN through the measurement of low concentrations of albumin in the urine. Some diabetic patients were found to have increased urinary albumin excretion rates (AER) not detectable by standard laboratory methods, and this condition was termed *microalbuminuria* (MA). Initial retrospective studies in type 1 diabetic patients (7–9) observed a risk of progression from MA to proteinuria of ~80% over the subsequent 6–14 years. These early studies, each of which used different AER criteria for MA, led to a consensus conference in which a general agreement was reached on the definition of MA (AER, 20–200 ng/min) (10). Since then, there has been broad acceptance of MA as a marker of increased DN risk. However, concern has been raised that there is a wide range of underlying diabetic glomerular lesions among long-standing type 1 diabetic patients (11,12). For some patients with persistent MA, renal lesions are quite advanced (11–13) and treatment for these patients could be less effective than at earlier stages of the disease. Thus, for these patients, MA may be a marker rather than a predictor of advanced renal structural changes. Therefore, it is not surprising that patients with MA may progress to proteinuria despite strict glycemic control

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ACEI, ACE inhibitors; AER, albumin excretion rates; DCCT, Diabetes Control and Complications Trial; DN, diabetic nephropathy; ESRD, end-stage renal disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; JDFI, Juvenile Diabetes Foundation International; MA, microalbuminuria; Vv(Mes/glom), mesangial fractional volume.

(14) and effective antihypertensive treatment. Thus, it would make sense to try to identify normoalbuminuric patients at increased DN risk in order to select those at early stages still amenable to aggressive intervention strategies such as strict glycemic control.

Although MA remains the best available marker for DN risk, we will review more recent studies suggesting that the percentage of MA patients progressing to proteinuria over ~10 years is 30–45%, much less than the initial reports of ~80% (7–9). Also, some MA patients may revert to normoalbuminuria. Although these differences may represent changes in the disease's natural history with improvements in treatment, MA is still a less precise predictor of DN risk than originally suggested. In fact, MA patients often have only mild diabetic renal injury (11,12), a finding consistent with a lower risk of progression from MA to proteinuria.

The presence of normal AER in long-standing diabetic patients has been said to identify patients at low risk of DN. However, a significant proportion of normoalbuminuric long-standing diabetic patients have well-established DN lesions (11,12), and ~40% of those who are ultimately at risk of progression to proteinuria are normoalbuminuric, despite many years of diabetes. Thus, it will be argued that AER, albeit the best currently available noninvasive predictor of DN risk, is unable to define patients who are safe from DN with an accuracy optimal for clinical decision making or for the design of certain clinical trials. For these reasons, it is suggested that investigations into new risk markers or into the combined use of several currently available markers may lead to important advances in this field.

METHODS

For a predictor of DN to be optimally useful, it should identify individuals at increased risk of the development of serious diabetic renal disease early enough in the natural history of the disorder that the evolution of the process can be influenced by intervention strategies. MA is uncommon in the first decade of type 1 diabetes, especially during the first 5 years (15–20), and by 20–25 years much of the natural history of the disorder has already declared itself within a patient population. Therefore, we used data derived from patients with 10–15 years of type 1 diabetes duration to determine the prevalence of normoalbuminuria, MA, and proteinuria in cross-sectional studies. Because the duration of type 2 diabetes is usually not accurately known, diabetes duration was not considered in the selection of prevalence data for our calculations. Longitudinal studies using AER as a predictor of the subsequent development of proteinuria and studies from which such information could be extracted (e.g., control populations in clinical trials) were also reviewed. We attempted to review all pertinent published articles in this area but, rather than performing meta-analyses, we selected those longitudinal studies for review which met the criteria outlined below. Omitted were articles with unorthodox definitions of MA, short follow-up times, or inadequate descriptions of the methods. It was considered important that patients be followed for at least 5 years from the baseline evaluation. This long follow-up was selected to improve the likelihood that the patient's final outcome would be reflected by the follow-up data. Shorter durations of follow-up were not extrapolated to longer follow-up times because data on patterns of progression of MA patients over time (e.g., linear and log linear) were not available. We divided these studies into 3 groups. Group A consisted of studies that adopted the consensus (10) definition of MA (AER of 20–200 μg/min in at least 2 of 3 sequential timed urine collections performed over 1–6 months) in which only patients with 5 or more years of follow-up were included. In group B studies, baseline AER was defined on the basis of a single urine sample and/or the follow-up was a mean or median of 5 years. Studies that would have been in group A or group B but that used different AER criteria to define MA were put in group C. Studies with a mean or median follow-up of <5 years were not included. Studies in type 1 diabetic patients were included only if baseline diabetes duration for all patients in these longitudinal studies was at least 7 years. We considered type 1 and type 2 diabetes studies separately.

TYPE 1 DIABETES

Diabetic nephropathy risk in normoalbuminuric type 1 diabetic patients. Three landmark studies placed the issue of AER measurements in diabetic patients at center stage. Two of the studies met the criteria for inclusion in this review (7,9), while 1 study included normoalbuminuric patients with as little as 1 year of diabetes duration at baseline (8). The 2 included studies were in group C (Table 1). One study found progression from normoalbuminuria to MA (defined as AER 15–150 μg/min) in ~14% (9) and another found progression to proteinuria in ~12% of patients (7).

Three studies were included in group A. Forsblom et al. (21), in a small well-designed study, found that ~7% of normoalbuminuric patients progressed to proteinuria and 14% to MA over 10 years of follow-up. Drs. Peter Rossing and Hans-Henrik Parving (personal communication), at our request, reanalyzed their extensive data based on criteria we imposed for group A studies. This study, which is by far the largest to date, found progression rates similar to those of Forsblom et al. (21) (Table 1). Moreover, there was no difference in diabetes duration at baseline in the patients remaining normoalbuminuric compared with those progressing to MA or proteinuria at follow-up. Mathiesen et al. (22) found somewhat lower progression rates (Table 1) but excluded some hypertensive patients. Interestingly, Mathiesen et al. noted that the rate of progression from normoalbuminuria to MA and proteinuria was almost constant throughout the 10 years of the study. The progression risk was somewhat lower in the normoalbuminuric younger patients of Chiarelli et al.'s study (23) (Table 1).

Drs. Michael Steffes and William Thomas facilitated our access to Diabetes Control and Complications Trial (DCCT) data. Normoalbuminuric patients randomized to conventional insulin treatment with at least 5 years of follow-up were selected for group B studies (DCCT, unpublished data). The DCCT used a single baseline urine sample for initial classification (14). Nonetheless, the DCCT results are identical to those of Rossing and Parving (Table 1). The study by Rudberg et al. (24) in children and adolescents showed somewhat higher rates of progression to MA (Table 1).

Based on these studies, we estimate that 5% of normoalbuminuric patients with at least 7 years of type 1 diabetes will progress to proteinuria over the next 5–10 years, whereas 17% will progress to MA. Progression from normoalbuminuria to proteinuria presumes at least the transient presence of MA. Thus, careful follow-up and repeated measures of AER are

TABLE 1
Risk of progression from normoalbuminuria to microalbuminuria or proteinuria in type 1 diabetic patients

Patient group and study	*n*	Diabetes duration (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of microalbuminuria (%)
Group A					
Forsblom et al. (21)	29	22.1 ± 5.4 (15–38)	10	6.9	13.8
Rossing and Parving (personal communication)	453	19.7 ± 9.3 (7–40)	9.0 ± 1.3 (5–10)	5	17
Mathiesen et al. (22)	209	17 ± 5 (10–30)	10	3.8	10
Chiarelli et al. (23)	170	~9.3 (7.1–23.2)	~8 (8.1–9.3)	0	10.6
Group B					
DCCT (unpublished data)	204	10.6 ± 2.3 (7–15)	6.8 ± 1.5 (5–9)	5	17
Rudberg et al. (24)	53	~11.5 >8	8	5.7	28.3
Group C					
Mogensen and Christensen (9)	29	— (7–19)	— (7–14)	0	13.8
Parving et al. (7)	17	15 ± 4 (10–24)	6	11.8	0

Data are *n*, %, or means ± SD (range).

necessary to detect increasing AER in these patients. In fact, studies show that AER values in the higher range of normoalbuminuria indicate greater risk of progression to MA (25), and these findings should be considered in clinical and clinical research settings.

Glomerular structure in normoalbuminuric type 1 diabetic patients. Glomerular structure is normal at onset of diabetes, and changes can be detected by morphometric measurements within 1.5–2.5 years after onset (26). However, because the normal range for glomerular structures, such as glomerular basement membrane (GBM) width or mesangial fractional volume (Vv[Mes/glom]) is quite wide, it may take some time for some individuals to progress from the normal to the abnormal range. However, glomerular changes in long-standing diabetes are always discernible as evidenced by direct comparison with measures from the patient's nondiabetic identical twin (27). Thus, all patients with type 1 diabetes appear to be developing glomerular structural changes of diabetes, albeit some at very slow rates. Others develop lesions so fast that they result in overt DN in as little as 10 years. Therefore, it is not surprising that long-standing normoalbuminuric type 1 diabetic patients have increased GBM width and Vv(Mes/glom) compared with age- and sex-matched nondiabetic normal control subjects. In the largest study performed (12), 66 nonproteinuric patients were divided into 4 groups on the basis of their AER as follows: I) normoalbuminuric with AER <15 μg/min, $n = 33$; II) low level MA with AER 15–30 μg/min, $n = 11$; III) MA with AER 31–70 μg/min, $n = 13$; and IV) MA with AER 71–150 μg/min, $n = 9$. Glomerular structural parameters were compared with 52 age- and gender-matched normal control subjects. Because MA is uncommon during the first decade of diabetes and the degree of glomerulopathy is directly related to the duration of diabetes (28), only patients with diabetes duration of at least 10 years were included. All parameters of glomerulopathy were abnormal in the normoalbuminuric group, although approximately half of the patients fell into the normal range. Figure 1 shows data on Vv(Mes/glom) in these patients, but similar results were obtained for GBM width. Note that in many of the group I (normoalbuminuric) patients, Vv(Mes/glom), the structural parameter most closely related to renal functional disturbances in diabetes (29), overlapped with values in patients in the MA groups (groups III and IV) and, in some instances, approached levels regularly associated with overt DN. Note also that several of the normoalbuminuric patients (group I) with Vv(Mes/glom) above the normal range had a reduced glomerular filtration rate (GFR) (<90 ml/min/1.73 m^2), hypertension, or both (Fig. 1). The combination of normoalbuminuria and reduced GFR is more likely to occur in type 1 diabetic women (30,31) and may be related to a self-selected low-protein diet. Whether some of these patients would have been MA on a normal protein diet is not known.

Other studies have shown that significant glomerular lesions can be present in normoalbuminuric patients. Berg et al. (32) found that 36 normoalbuminuric adolescents (median diabetes duration 10.8 years, range 7.5–19.2) had greater GBM width and mesangial matrix fractional volume than normal control subjects, but Berg et al. did not report an increase in Vv(Mes/glom) in these patients with approximately half of the diabetes duration of our cohort (12). Using pooled data from

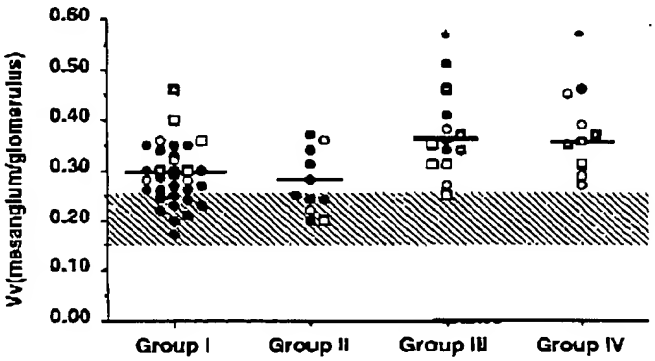

FIG. 1. Mesangial fractional volume (Vv[mesangium/glomerulus]) in the 4 groups of patients. The shaded area represents the means ± 2 SD in a group of 52 age-matched normal control subjects. ●, Normal BP and GFR; ○, reduced GFR (<90 ml · min^{-1} · 1.73m^{-2}); □, hypertension (≥140/85); ⊠, reduced GFR and hypertension. *$P < 0.005$ vs. groups I and II (12).

TABLE 2
Risk of progression from microalbuminuria to proteinuria in type 1 diabetic patients

Patient group and study	*n*	Diabetes duration (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of normoalbuminuria (%)
Group A					
Forsblom et al. (21)	20	25.7 ± 5.7 (16–36)	10	25	35
Rossing and Parving (personal communication)	132	20.3 ± 8.7 (7–40)	9.1 ± 1.3 (5–10)	30	20
Group B					
DCCT (unpublished data)	30	11.4 ± 2.3 (7–15)	7.3 ± 1.6 (5–9)	23	43
Rudberg et al. (24)	11	~11.5 >8	8	18.2	36.4
Group C					
Mogensen and Christensen (9)	14	— (7–19)	~10 (7–14)	85.7	7.1
Viberti et al. (8)	8	14.1 ± 2.9 (7–33)	14	87.5	0
Parving et al. (7)	8	19 ± 5 (13–25)	6	62.5	25

Data are *n*, %, or means ± SD (range).

several studies from her laboratories, Østerby (28) described an increase in GBM width in normoalbuminuric type 1 diabetic patients, whereas Vv(Mes/glom) was similar in control subjects and normoalbuminuric patients. However, the differences in our results (12) compared with Østerby's (28) results are best explained by the marked differences in duration of diabetes in the 2 groups of normoalbuminuric patients (12 years in the Aarhus cohort versus 21 years in the Minnesota cohort). It should also be pointed out that the results of the normoalbuminuric patients shown in Fig. 1 were confirmatory of our earlier study (11). However, different structural definitions were used in our earlier study (11), and this has led to some confusion in the interpretation of our results (32a). In fact, our findings of advanced lesions in some normoalbuminuric patients are also entirely consistent with the natural history data previously described. Thus, it is not surprising that some patients, who are normoalbuminuric after many years of type 1 diabetes but have advanced glomerular lesions, may progress to MA and proteinuria. In fact, in a preliminary 5- to 17-year follow-up study of normoalbuminuric patients with long-standing diabetes, we found that those progressing to MA or proteinuria had worse glomerular lesions at baseline than those who remained normoalbuminuric (33). The increase in AER at early clinical stages is related primarily to increasing Vv(Mes/glom). Thus, we previously showed that changes in AER over 5 years correlated with changes in Vv(Mes/glom) over this time, but not with other structural variables (34).

Diabetic nephropathy risk in microalbuminuric type 1 diabetic patients. The 3 original articles (7–9) on this subject studied a total of 30 patients, used 3 different ranges of AER to define MA, may have used post hoc methods to select those ranges, and included some patients whose baseline status was defined by a single urine sample (7,8). Progression to proteinuria from MA over 6–14 years occurred in ~80% of these patients (group C) (Table 2).

The prospective study by Forsblom et al. (21) suggested that these 3 initial studies may have overestimated the risk of progression from MA to proteinuria. This study evaluated 20 MA type 1 diabetic patients with 16–36 years of diabetes duration using group A criteria (Table 2) and found progression to proteinuria 10 years later in only 25%, whereas 35% reverted to normoalbuminuria and 40% remained microalbuminuric. One argument that could be raised against the conclusions of this study is that by selecting patients with at least 15 years of disease duration, the study was biased toward patients less likely to progress, because most patients destined to develop proteinuria will do so before 20 years of duration. Drs. Peter Rossing and Hans-Henrik Parving (personal communication) performed analyses that we requested on their extensive patient population and permitted the use of the data for this review (Table 2). Using group A criteria, they followed 132 MA patients with 20.3 ± 8.7 (range 7–40) years' duration for a mean of 9.1 years. Thirty percent had developed proteinuria, 20% became normoalbuminuric, and 50% remained microalbuminuric at follow-up. Duration of diabetes was, in fact, shorter at baseline in those with MA progressing to proteinuria (17 ± 8 years) than those remaining with MA (22 ± 9 years, $P < 0.005$) but was not different from those becoming normoalbuminuric (20 ± 9 years). These data are consistent with an earlier abstract by Rossing et al. (35) indicating a 45% risk of progression to proteinuria in MA patients with <15 years of diabetes duration vs. 26% progression rate in patients with >15 years' duration. Indeed, these studies confirmed Forsblom et al.'s (21) observations of a 25% risk of progression of patients with 15 or more years of diabetes duration. Interestingly, data extracted from conventionally treated MA DCCT patients (group B) (Table 2) revealed progression rates to proteinuria similar to those of the group A studies (Table 2). However, duration of diabetes in this DCCT cohort was 7–15 years and progression to proteinuria was only 23%. This was less than the 45% progression rate in the similar but much larger cohort of Rossing et al. (35). These differences could be due to the less rigorous definition of MA at baseline in the DCCT study or could represent population differences. Rudberg et al. (24) found an even lower progression rate (18.2%) (Table 2) in MA children and adolescents. The reason for this is not clear, but it may be age related (see also Chiarelli et al [23], Table 1) or a consequence of the small sample size.

Based on these more recent studies, we estimate the rate of progression from MA to proteinuria over 5–10 years to be ~30%, perhaps 15% higher in patients with <15 years' dia-

TABLE 3
Risk of progression from normoalbuminuria to microalbuminuria or proteinuria in type 2 diabetic patients

Patient group and study	*n*	Age (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of microalbuminuria (%)
Group A					
Forsblom et al. (39)	108	~58 (35–70)	9	8.3	20.4
Tanaka et al. (40)	74	~61 (60–75)	6	0	32.4
Ravid et al. (41)	97	54.4 ± 2.9 (38–59)	6	0	15.5
Group B					
Gall et al. (43)	191	55 (20–65)	5.8 (1.5–6.0)	2.6	18.8
Ravid et al. (44)	621	47.7 ± 4.5 (40–60)	7.8 ± 0.9 (2–9)	14.5	17.9
Group C					
Mogensen (38)	128	~66 (50–75)	10	5.5	—
Kawazu et al. (45)	33	~54	8	0	57.6
Jerums et al. (46)	51	57 ± 7.1	6.4 ± 2.1 (3–10.3)	11.8	5.9
Haneda et al. (47)	34	~57	5	2.9	29.4
Niskanen et al. (48)	92	~56 (45–64)	5	0	10.9

Data are *n*, %, or means ± SD (range).

betes duration, but considerably lower than originally estimated. It is possible, of course, that with a follow-up >10 years, more MA patients would progress to proteinuria. However, it is also possible that more progression would be seen with longer follow-up in the normoalbuminuric patients. These long-term data are needed but are currently not available. One hypothesis that could explain these reduced progression rates is the recent change in the natural history of this disorder based on newer treatment strategies such as improved systemic blood pressure control. Although currently available data are not conclusive, Drs. Rossing and Parving did not find a different rate of return to normoalbuminuria from MA in patients treated or not treated with antihypertensive medications (P. Rossing, H-H. Parving, personal communication), including ACE inhibitors (ACEI). Another suggestion is that overall management of glycemia has improved since the original observations. There are no studies with adequate statistical power to address this hypothesis with confidence. Nonetheless, the DCCT could not demonstrate that improved glycemia has a beneficial effect on the risk of progression from MA to proteinuria (14).

Glomerular structure in microalbuminuric type 1 diabetic patients. Unlike the controversies regarding normoalbuminuric patients, there is general consensus that, on average, MA patients have increased GBM width and Vv(Mes/glom) compared with normoalbuminuric patients (11–13,36) and control subjects (11–13). However, all studies have shown wide ranges of glomerular structure among type 1 diabetic patients with MA. Thus, GBM width ranges from the upper limits of normal to markedly increased. Moreover, there is no significant increase in GBM width in patients with different levels of MA (12). The same is true for Vv(Mes/glom) (Fig. 1) when the values in MA patients in groups III and IV ranged from the upper limits of normal (12) to levels that overlapped with those observed in patients with proteinuria (P.F., M.M., unpublished data). The values in the patients in groups III and IV were greater than in patients with lower levels of increased AER (15–30 μg/min, group II) and normoalbuminuric patients (group I), whereas groups I and II overlapped completely (12). Østerby (28) found some MA patients with Vv(Mes/glom) in the normal range. We also found this to be true when patients with AER in the range of 15–30 μg/min were examined (group II) (Fig. 1). However, at higher levels of MA, Vv(Mes/glom) was increased in virtually all patients. Also, we found that patients with AER >30 μg/min had a relatively high incidence of hypertension, decreased GFR (<90 ml · min^{-1} · 1.73 m^{-2}), or both (12). Nonetheless, even among these patients, the range of Vv(Mes/glom) was quite wide and the values in the MA patients overlapped with those of the normoalbuminuric patients (Fig. 1). In longitudinal studies of MA patients, Bangstad et al. (37) found that GBM width at baseline biopsy was predictive ($r^2 = 0.67$, $P < 0.0001$) of AER after 6 years of follow-up, whereas Vv(Mes/glom) was a significant but less precise predictor.

In summary, the presence of serious diabetic glomerular lesions in some normoalbuminuric patients suggests that altered glomerular permeability to proteins is not a necessary precondition for the development of these lesions. It is unlikely that established diabetic glomerular lesions are of little prognostic value in normoalbuminuric patients. On the contrary, preliminary studies indicate a greater risk of progression in normoalbuminuric patients with more advanced lesions (33). The risk of progression to proteinuria over the next decade of long-standing type 1 diabetic patients with persistent MA is less than originally estimated. Moreover, approximately one-third of MA patients will return to normoalbuminuria. On the other hand, because 5% of long-standing normoalbuminuric patients will be proteinuric and 17% will be microalbuminuric after 5–10 years of follow-up, and because ~75% of long-standing type 1 diabetic patients will be normoalbuminuric at initial evaluation (15–19), one can estimate that 40% of those patients at risk of DN will be normoalbuminuric at baseline. This variable outcome could reflect the wide range of glomerular structural measures seen among normoalbuminuric and MA patients; however, this hypothesis has not been adequately tested. Finally, these observations should be taken into account in discussing prognosis with individual patients and, perhaps, in making decisions about treatment. Certainly, these data must be

TABLE 4
Risk of progression from microalbuminuria to proteinuria in type 2 diabetic patients

Patient group and study	*n*	Age (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of normoalbuminuria (%)
Group A					
Tanaka et al. (40)	49	~65 (60–75)	6	53.1	0
Ravid et al. (52)	52	44.8 ± 3.5 (36–49)	5	36.5	—
Ahmad et al. (53)	58	50.3 ± 2.1 (45–55)	5	20.7	—
Group B					
Gall and Parving (personal communication)	86	58 (28–65)	5	34.8	—
Group C					
Mogensen (38)	76	~66 (50–75)	10	22.4	—
Yajima et al. (54)	59	—	9	35.6	—
Kawazu et al. (45)	15	~56	8	40	0
Haneda et al. (47)	18	—	5	33.3	0
Niskanen et al. (48)	21	~56 (45–64)	5	0	42.9

Data are *n*, %, or means ± SD (range).

carefully considered when designing intervention trials for MA patients.

TYPE 2 DIABETES

Diabetic nephropathy risk in normoalbuminuric type 2 diabetic patients. Mogensen (38) first studied the prognostic value of AER in type 2 diabetic patients (Table 3). AER was measured on spot urines and on single samples from 32% of the case subjects. In this 10-year retrospective study, MA was defined as urinary albumin concentration of 30–140 μg/ml. Progression from normoalbuminuria to proteinuria occurred in 5.5% of these patients. The risk of progression to MA was not stated. The 48% death rate in these initially normoalbuminuric patients was remarkably high. Thus, the data from this study could not be used to estimate the risk of renal progression among normoalbuminuric type 2 diabetic patients.

For this review, we used the 3 published reports that met the group A studies' criteria except for duration, which cannot be accurately determined in type 2 diabetic patients (Table 3). These studies (39–41) followed patients for 6 to 9 years from the baseline AER measurement and found a .5–30% incidence of progression from normoalbuminuria to MA and from 0 to 8% from normoalbuminuria to proteinuria. Table 3 excludes 1 study with similar outcomes in which >20% of case subjects were lost during follow-up (42).

Two papers were categorized in group B. One produced similar (43) and the other produced higher values (44) of progression to proteinuria than the group A studies (Table 3). Five papers (38,45–48) were in group C because of the MA definition used (Table 3). Progression from normoalbuminuria to MA varied markedly from 5.9 to 57.6%, whereas progression from normoalbuminuria to proteinuria varied from 0 to 11.8%. Only the data from group A studies were used for the risk calculation.

Glomerular structure in normoalbuminuric type 2 diabetic patients. There are few published papers on renal structure in normoalbuminuric type 2 diabetic patients compared with control subjects, so information was also extracted from published abstracts.

The rate of development of DN lesions is less clear in type 2 compared with type 1 diabetic patients because, with the exception of the Pima Indian studies (49), duration is usually not precisely established in these patients. Nonetheless, GBM width and Vv(Mes/glom) are increased in normoalbuminuric Caucasian (50), Pima Indian (49), and Japanese (51) long-term type 2 diabetic patients. As in type 1 diabetic patients, there is considerable overlap with normal control subjects, and some normoalbuminuric type 2 diabetic patients have relatively advanced glomerular lesions (50,51). Thus, as is true for type 1 diabetic patients, there is a structural basis for explaining the progression to MA and proteinuria among some normoalbuminuric type 2 diabetic patients. Whether normoalbuminuric type 2 diabetic patients with more advanced diabetic renal lesions are at greater risk of progression needs to be determined. In Pima Indians, glomerular structure was not different in MA patients compared with normoalbuminuric patients with long diabetes duration, whereas MA patients had more advanced glomerulopathy than normoalbuminuric patients with short duration. These results might explain the observation that some long-term normoalbuminuric patients are at high risk of progression. Further, as discussed below, there are more varied renal structural patterns and patterns of functional progression among microalbuminuric, and also proteinuric, type 2 diabetic patients compared with type 1 diabetic patients, and the final outcome of these patients remains to be fully established.

Diabetic nephropathy risk in microalbuminuric type 2 diabetic patients. For reasons outlined above, the initial retrospective examination of outcomes in 76 MA type 2 diabetic patients by Mogensen (38) was a group C study (Table 4). MA patients in this study had a 77.6% 10-year mortality rate, mostly from cardiovascular disease, whereas 22% progressed to proteinuria.

Subsequently, 3 prospective group A studies (40,52,53) with much lower mortality rates among MA type 2 diabetic patients have been published. These studies included a total of 159 MA patients followed for 5–6 years with an average risk of progression to proteinuria of ~40% (Table 4). The risk of proteinuria over a longer term follow-up is not known but is presumably greater. One of these studies (40) reported that no patients were normoalbuminuric at follow-up (Table 4). The other 2 studies (52,53) did not provide these data.

One group B study evaluating 86 MA patients (M.-A. Gall, H.-H. Parving, personal communication) observed, after 5 years of follow-up, approximately the same progression rate to proteinuria as seen in group A studies, but return to normoalbuminuria was not defined in this cohort (Table 4). Five studies were classified as group C because of MA definitions (38,45,47,48,54) (Table 4). In these studies, the progression rates from MA to proteinuria ranged from 0 to 40%, and these articles were not used in the risk calculations.

Glomerular structure in microalbuminuric type 2 diabetic patients. Caucasian type 2 diabetic patients with MA have more complex patterns of renal structural changes than MA type 1 diabetic patients. A light microscopic study of 34 unselected MA type 2 diabetic patients described that 10 (29.4%) had normal or near-normal renal structure (55), a finding uncommon in type 1 diabetes. Ten patients had renal structural changes typical of those seen in type 1 diabetic patients with more or less balanced severity of glomerular, tubulointerstitial, vascular, and global glomerulosclerosis lesions. However, 14 subjects (41.2%) had atypical patterns of renal injury with absent or only mild diabetic glomerular changes associated with other disproportionately severe renal structural changes, including important tubulointerstitial lesions with or without arteriolar hyalinosis and with or without increased global glomerular sclerosis. Patients with proliferative retinopathy all had typical and well-established glomerulopathy lesions. None of the patients without retinopathy had typical lesions. However, background retinopathy could be associated with any of the 3 structural categories defined above. These studies were confirmed by electron microscopic observations (56) showing that MA type 2 diabetic patients more frequently had electron microscopic morphometric glomerular structural measures in the normal range and, as a group, had less severe lesions than MA type 1 diabetic patients. Many of these observations have been confirmed in Japanese type 2 diabetic patients (51). On the other hand, Pima Indian type 2 diabetic patients at very high risk of ESRD from diabetes appear to have lesions more similar to those seen in type 1 diabetic patients. One study has argued that the underlying pattern of renal injury does not predict the rate of GFR decline among a Caucasian cohort of already proteinuric type 2 diabetic patients (57). In contrast, a large 4.3-year follow-up study of ACEI-treated Caucasian type 2 diabetic patients with MA and proteinuria observed that patients with more rapid GFR decline had greater GBM width and Vv(Mes/glom) at baseline (58).

In summary, assuming the risk of progression from MA to proteinuria in type 2 diabetic patients to be ~40% (Table 4), then the risk of developing proteinuria over the next 10–15 years in normoalbuminuric type 2 diabetic patients would be ~12% (Table 3). Based on studies of >6,000 patients, ~70% of screened type 2 diabetic patients are normoalbuminuric (42,59–67). It can then be estimated that ~40% of the dipstick-negative type 2 diabetic patients who are ultimately destined to develop proteinuria will be normoalbuminuric at initial screening, whereas ~60% will be microalbuminuric. Thus, the predictive value of AER below the range of overt proteinuria appears to be similar among type 1 and type 2 diabetic patients. This similarity in prognostic value of AER emerges despite the fact that knowledge of duration in type 2 diabetes is less precise than in type 1 diabetes, and the follow-up period in the type 2 diabetes studies has tended to be shorter than in type 1 studies. Whether risk of progression in type 2 diabetic patients would be even greater if the follow-up period were extended is an important but unanswered question. The study of type 2 diabetes is further complicated by the findings of greater renal structural heterogeneity among type 2 diabetic patients than type 1 MA and proteinuric patients (50,51,56,68). The regularity with which type 2 diabetic patients with proteinuria progress to ESRD is less well known than for type 1 diabetic patients. Nelson et al. (69) suggested that the rate of decline of GFR among type 2 diabetic Pima Indian patients is similar to that of Caucasian type 1 diabetic patients. However, in contrast to Pima Indians and type 1 diabetic patients, some proteinuric Caucasian and Japanese type 2 diabetic patients have normal or near-normal glomerular structure and they seem not to progress toward ESRD at the same rate as patients with advanced lesions (58). At any rate, the prognostic value of proteinuria is less clear in type 2 diabetes versus type 1 diabetes and, consequently, so is the meaning of progression from MA to proteinuria in these patients. The higher cardiovascular death rate among type 2 diabetic patients with MA may further obscure nephropathy risk. There is also a higher incidence of hypertension among normoalbuminuric and microalbuminuric type 2 diabetic patients compared with type 1 diabetic patients. On one hand, left untreated, this could superimpose hypertensive renal injury on the diabetic nephropathy lesions. Theoretically, hypertension could also accelerate diabetic lesions. Further, hypertension could be associated with increased urinary AER (70–72). Thus, the greater incidence of hypertension in type 2 diabetic patients could complicate the predictive value of AER for DN risk in these patients. On the other hand, antihypertensive treatment with drugs, such as ACEI, could directly influence AER (73) and obscure outcomes defined by this measure. Finally, racial factors may have greater influence in nephropathy risk in type 2 diabetes than in type 1 diabetes (74). Perhaps even more than for type 1 diabetes, examination of renal structure may provide a substantial basis for understanding the heterogeneity in outcome among type 2 diabetic patients with MA. For these reasons, it is considered vital that well-designed large longitudinal natural history and renal biopsy studies be carried out among various ethnic and racial groups with type 2 diabetes. It is worth reiterating that >35% of all new ESRD patients in the U.S. have type 2 diabetes, yet their underlying renal disease is still poorly understood.

NEED FOR NEW MARKERS AND PREDICTORS OF DIABETIC NEPHROPATHY RISK

DN has rapidly become an important public health problem. Early detection of risk leading to the possibility of intervention before advanced renal damage has occurred is an obviously important goal. This goal is made difficult by the fact that much of the important diabetic renal structural injury can occur in absolute clinical silence. It may not be practical to treat all diabetic patients with all potentially useful therapies (e.g., strict glycemic control and antihypertensive medications), because of issues of cost and inadequate health care infrastructure, and because those without risk of renal complications would be needlessly exposed to the risk of these treatments. It would be far better to focus the available health care resources on those most likely to benefit. Measurement of AER in the subproteinuric range has been a very

important advance in this field. This review confirms that AER is the strongest broadly available marker or predictor of DN risk. However, we need improved markers and predictors of DN risk. These will be addressed in 2 general categories as follows: *1*) better use of existing methods and *2*) development of new technologies.

Existing methods. Longitudinal studies are indicated in type 1 and type 2 diabetes, which would examine the potential value of using repeated measures of AER over time, different set points for the definition of MA, or both. In addition, the combination of measures of AER with multiple clinical and renal structural parameters may lead to the development of more precise risk estimates for DN. These additional variables could include age, diabetes duration, blood pressure (including 24-h blood pressure monitoring), GFR, HbA_{1c}, retinopathy, and renal biopsy measurements. Prospective studies in type 1 and type 2 diabetic patients generally support the concept that normoalbuminuric and MA patients who progress have significantly higher baseline levels of blood pressure (25,39,43,44,47,75–77) and HbA_{1c} (14,21,22,25, 39,40,43–45,47,77–79) compared with patients that do not progress. However, there is still controversy as to whether increased baseline GFR is a predictor of progression (9,24,80–85). Preliminary results of our prospective study in normoalbuminuric type 1 diabetic patients have shown that patients who progress to MA or proteinuria have worse baseline glomerular lesions, lower GFR, and are more frequently hypertensive than patients remaining normoalbuminuric (33). Other variables, in a list by no means meant to be exhaustive, could include plasma prorenin (86,87), erythrocyte sodium/lithium countertransport activity (23), lipid levels, smoking history, and family history of cardiovascular disease and DN. A multivariate risk-assessment scheme far more exact than AER alone could emerge from such studies.

Development of new technologies. New tests are needed to provide accurate DN risk estimates before renal functional disturbances are well established (88). Initially, these tests will need to be validated, at least in part, by their association with important renal lesions as ascertained in renal biopsies. If sufficiently precise, these early predictors could obviate the need for renal biopsy except as a research tool. There are many possibilities for such new approaches to this problem and only a few are suggested as follows: *1*) identification of genes associated with increased or decreased DN risk; *2*) measures of substances in blood or urine, such as extracellular matrix molecules, products of glycation, or growth factors; *3*) measurements of tubular function; *4*) measurements of cellular functions (e.g., in cultured skin fibroblasts), which may be associated with DN risk, including extracellular matrix molecules and growth factors; *5*) less invasive methods such as fine needle aspiration to sample renal tissues for structural or biochemical changes associated with nephropathy risk; and *6*) development and application of new imaging technologies (e.g., positron emission tomography and magnetic resonance imaging) as tools to detect early renal diabetic biochemical or structural changes.

CONCLUSIONS

The measurement of urinary AER has led to very important advances in the field of DN. AER is currently the best available noninvasive means of following the course of kidney disease in nonproteinuric diabetic patients; therefore, this review strongly supports the current recommendation that urinary AER should be monitored on a regular basis, in accordance with accepted protocols and procedures (89,90). Moreover, given their increased risk of progression, patients with persistent MA should be considered for antihypertensive therapy and improved glycemic control. However, concerns have been previously raised (39,51,91), and this study concurs, that AER does not predict DN risk with the accuracy suggested by the original studies in this field (7–9) and that changes in the natural history of this disease may not fully explain these discrepancies. Moreover, AER as a predictor in nonproteinuric diabetic patients may not be sufficient for optimal clinical decision making, clinical research design, or public health policy development. Improved predictors could come from existing methodologies or from technologies not yet fully developed. The growing magnitude of the DN problem and its huge human and social costs mandate that we commit far greater basic and clinical research resources to this problem. The value of long-term continuous research support can be seen in the use by the National Institutes of Health of intramural funding studies of the Pima Indian population, and this concept should be expanded to the study of other important patient groups. This need is dictated by the very long and largely silent natural history of DN, and this natural history will not be changed by wishful thinking.

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REFERENCES

1. 1999 United States Renal Data System Annual Report: National Technical Information Service. US Department of Health and Human Services, Springfield, VA
2. Bojestig M, Arnqvist HJ, Hermansson G, Karlberg BE, Ludvigsson J: Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 330:15–18, 1994
3. Rossing P, Rossing K, Jacobsen P, Parving HH: Unchanged incidence of diabetic nephropathy in IDDM patients. *Diabetes* 44:739–743, 1995
4. Mogensen CE: Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J* 285:685–688, 1982
5. Parving H-H, Andersen AR, Smidt UM, Svendsen PA: Early and aggressive antihypertensive treatment reduces the rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1179, 1983
6. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: the Collaborative Study Group. *N Engl J Med* 329:1456–1462, 1993
7. Parving H-H, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR: Early detection of patients at risk of developing diabetic nephropathy: a longitudinal study of urinary albumin excretion. *Acta Endocrinol (Copenh)* 100:550–555, 1982
8. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1:1430–1432, 1982
9. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 311:89–93, 1984
10. Mogensen CE, Chachati A, Christensen CK, Close CF, Deckert T, Hommel E, Kastrup J, Lefebvre P, Mathiesen ER, Feldt-Rasmussen B, Schmitz A, Viberti GC: Microalbuminuria: an early marker of renal involvement in diabetes. *Uremia Invest* 9:85–95, 1985–1986

11. Chavers BM, Bilous RW, Ellis EN, Steffes MW, Mauer SM: Glomerular lesions and urinary albumin excretion in type I diabetic patients without overt proteinuria. *N Engl J Med* 320:966–970, 1989
12. Fioretto P, Steffes MW, Mauer SM: Glomerular structure in nonproteinuric insulin-dependent diabetic patients with various levels of albuminuria. *Diabetes* 43:1358–1364, 1994
13. Bangstad HJ, Østerby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Nyberg G, Frahm Bjorn S, Hanssen KF: Early glomerulopathy is present in young type 1 (insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 36:523–529, 1993
14. The Diabetes Control and Complications Trial Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 47:1703–1720, 1995
15. Parving H-H, Hommel E, Mathiesen E, Skøtt P, Edsberg B, Bahnsen M, Lauritzen M, Hougaard P, Lauritzen E: Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. *Br Med J* 296:156–160, 1988
16. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 39:1116–1124, 1990
17. Mangili R, Deferrari G, DiMario U, Ciampietro O, Navalesi R, Nosadini R, Rigamonti G, Spezia R, Crepaldi G: Arterial hypertension and microalbuminuria in IDDM: the Italian Microalbuminuria Study. *Diabetologia* 37:1015–1024, 1994
18. Olsen BS, Johannesen J, Sjolie AK, Borch-Johnsen K, Hougaard P, Thorsteinsson B, Pramming S, Martinelli K, Mortensen HB, the Danish Study Group of Diabetes in Childhood: Metabolic control and prevalence of microvascular complications in young patients with type 1 diabetes mellitus. *Diabet Med* 16:79–85, 1999
19. Warram JH, Gearin G, Laffel L, Krolewski AS: Effect of duration of type 1 diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 7:930–937, 1996
20. Microalbuminuria Collaborative Study Group: Microalbuminuria in type 1 diabetic patients: prevalence and clinical characteristics. *Diabetes Care* 15: 495–501, 1992
21. Forsblom CM, Groop P-H, Ekstrand A, Groop LC: Predictive value of microalbuminuria in patients with insulin dependent diabetes of long duration. *BMJ* 305:1051–1053, 1992
22. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T: The natural course of microalbuminuria in insulin dependent diabetes: a 10-year prospective study. *Diabet Med* 12:482–487, 1995
23. Chiarelli F, Catino M, Tumini S, Martino M, Mezzetti A, Varrotti A, Vanelli M: Increased Na^+/Li^+ countertransport activity may help to identify type 1 diabetic adolescents and young adults at risk for developing persistent microalbuminuria. *Diabetes Care* 22:1158–1164, 1999
24. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy: an 8-year prospective study. *Kidney Int* 41:822–828, 1992
25. Microalbuminuria Collaborative Study Group: Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: a seven-year prospective study. *Diabet Med* 16:918–925, 1999
26. Østerby R: Morphometric studies of the peripheral glomerular basement membrane in early juvenile diabetes. I. Development of initial basement membrane thickening. *Diabetologia* 8:84–92, 1972
27. Steffes MW, Sutherland DER, Goetz FC, Rich SS, Mauer SM: Studies of kidney and muscle biopsy specimens from identical twins discordant for type I diabetes mellitus. *N Engl J Med* 312:1282–1287, 1985
28. Østerby R: Glomerular structural changes in type 1 (insulin-dependent) diabetes mellitus: causes, consequences, and prevention. *Diabetologia* 35:803–812, 1992
29. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC: Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 74:1143–1155, 1984
30. Lane PH, Steffes MW, Mauer M: Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. *Diabetes* 41:581–586, 1992
31. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G: Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 43:649–655, 1994
32. Berg UB, Torbjörnsdotter TB, Jaremko G, Thalme B: Kidney morphological changes in relation to long-term renal function and metabolic control in adolescents with IDDM. *Diabetologia* 41:1047–1056, 1998

32a. Mogensen CE: Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. Diabetologia 42:263–285, 1999

33. Caramori ML, Fioretto P, Mauer M: Long-term follow-up of normoalbuminuric longstanding type 1 diabetic patients: progression is associated with worse baseline glomerular lesions and lower glomerular filtration rate (Abstract). *J Am Soc Nephrol* 10:126A, 1999
34. Fioretto P, Steffes MW, Sutherland DER, Mauer M: Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression. *Kidney Int* 48:1929–1935, 1995
35. Rossing P, Hougaard P, Borch-Johnsen K, Parving H-H: Progression from microalbuminuria to diabetic nephropathy in IDDM (Abstract). *J Am Soc Nephrol* 8:117A, 1997
36. Walker JD, Close CF, Jones SH, Rafferty M, Keen H, Viberti GC, Østerby R: Glomerular structure in type 1 (insulin-dependent) diabetic patients with normo- and microalbuminuria. *Kidney Int* 41:741–748, 1992
37. Bangstad HJ, Østerby R, Hartmann A, Berg TJ, Hanssen KF: Severity of glomerulopathy predicts long-term urinary albumin excretion rate in patients with type 1 diabetes and microalbuminuria. *Diabetes Care* 22:314–319, 1999
38. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
39. Forsblom CM, Groop P-H, Ekstrand A, Totterman KJ, Sane T, Saloranta C, Groop L: Predictors of progression from normoalbuminuria to microalbuminuria in NIDDM. *Diabetes Care* 21:1932–1938, 1998
40. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tobjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
41. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R: Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 128:982–988, 1998
42. John L, Sunder Rao PSS, Kamagasabapathy AS: Rate of progression of albuminuria in type II diabetes: five-year prospective study from South India. *Diabetes Care* 17:888–890, 1994
43. Gall MA, Hougaard P, Borch-Johnsen K, Parving H-H: Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 314:783–788, 1997
44. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R: Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med* 158:998–1004, 1998
45. Kawazu S, Tomono S, Shimizu M, Kato N, Ohno T, Ishii C, Murata K, Watanabe T, Negishi K, Suzuki M, Takahashi M, Ishii J: The relationship between early diabetic nephropathy and control of plasma glucose in non-insulin-dependent diabetes mellitus: the effect of glycemic control on the development and progression of diabetic nephropathy in an 8-year follow-up study. *J Diabetes Complications* 8:13–17, 1994
46. Jerums G, Cooper ME, Seeman E, Murray RML, McNeil J: Spectrum of proteinuria in type I and type II diabetes. *Diabetes Care* 10:419–427, 1987
47. Haneda M, Kikkawa R, Togawa M, Koya D, Kajiwara N, Uzu T, Shigeta Y: High blood pressure is a risk factor for the development of microalbuminuria in Japanese subjects with non-insulin-dependent diabetes mellitus. *J Diabetes Complications* 6:181–185, 1992
48. Niskanen L, Uusitupa M, Siitonen O, Voutilainen E, Penttilä I, Pyörälä K: Microalbuminuria predicts the development of serum lipoprotein abnormalities favoring atherogenesis in newly diagnosed type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 33:237–243, 1990
49. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, Coplon NS, Sun L, Meyer TW: Podocyte loss and progressive glomerular injury in type II diabetes. *J Clin Invest* 99:342–348, 1997
50. Fioretto P, Mauer M, Velussi M, Carraro A, Muollo B, Baggio B, Crepaldi C, Nosadini R: Ultrastructural measures of glomerular extracellular matrix accumulation in non-proteinuric type 2 diabetic patients (Abstract). *J Am Soc Nephrol* 7:1356–1357, 1996
51. Moriya T, Moryia R, Yajima Y, Steffes MW, Mauer M: Urinary albumin is a weaker predictor of diabetic nephropathy lesions in Japanese NIDDM patients than in Caucasians IDDM patients (Abstract). *J Am Soc Nephrol* 8:116A, 1997
52. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 118:577–581, 1993
53. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 20:1576–1581, 1997
54. Yajima Y, Jim Y, Moriya T, Maroba K: Progression from microalbuminuria to overt nephropathy in NIDDM: the receiver operating characteristics curve

analysis (Abstract). *Diabetologia* 41 (Suppl. 1):A287, 1998
55. Fioretto P, Mauer M, Brocco E, Velussi M, Frigato F, Muollo B, Sambataro M, Abaterusso C, Baggio B, Crepaldi G, Nosadini R: Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 39:1569–1576, 1996
56. Fioretto P, Mauer M, Bortoloso E, Barzon I, Saller A, Della Vestra M, Abaterusso C, Baggio B, Nosadini R: Glomerular ultrastructure in type 2 diabetes (Abstract). *J Am Soc Nephrol* 9:114A, 1998
57. Ruggenenti P, Gambara V, Perna A, Bertani T, Remuzzi G: The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol* 9:2336–2343, 1998
58. Nosadini R, Velussi M, Brocco E, Bruseguin M, Abaterusso C, Saller A, Della Vestra M, Carraro A, Bortoloso E, Sambataro M, Barzon I, Frigato F, Muollo B, Chiesura-Corona M, Pacini G, Baggio B, Piarulli F, Sfriso A, Fioretto P: Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes* 49:476–484, 2000
59. Verthoeven S, van Ballegooie E, Casparie AF: Impact of late complications in type 2 diabetes in a Dutch population. *Diabet Med* 8:435–438, 1991
60. Bruno G, Cavallo Perin P, Bargero G, Borra M, Calvi V, Derrico N, Deambrogio P, Pagano G: Prevalence and risk factors for micro- and macroalbuminuria in an Italian population-based cohort of NIDDM subjects. *Diabetes Care* 19:43–47, 1996.
61. Plehlmeier W, Renner R, Schramm W, Kimmerling T, Garbe S, Proetzch R, Fahn J, Piwernetz K, Landgraf R: Screening of diabetic patients for microalbuminuria in primary care: the PROSIT-Project Proteinuria Screening and Intervention. *Exp Clin Endocrinol Diabetes* 107:244–251, 1999
62. Klein R, Klein BE, Moss SE: Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 16:1325–1330, 1993
63. Gall MA, Rossing P, Skott P, Damsbo P, Vaag A, Bech K, Deigaard A, Lauritzen M, Lauritzen E, Hougaard P, Beck-Nielsen H, Parving H-H: Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 34:655–661, 1991
64. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes: a 10-year follow-up study of 503 patients. *Diabet Med* 5:126–134, 1988
65. Esmatjes E, Castell C, Gonzales T, Tresseras R, Lloveras G: Epidemiology of renal involvment in type II diabetics (NIDDM) in Catalonia: the Catalan Diabetic Nephropathy Study Group. *Diabetes Res Clin Pract* 32:157–163, 1996
66. Delcourt C, Vauzelle Kervroedan F, Cathelineau G, Papoz L: Low prevalence of long-term complications in non-insulin dependent diabetes mellitus in France: a multicenter study: CODIAB-INSERM-ZENECA Pharma Study Group. *J Diabetes Complications* 12:88–95, 1998
67. Torffvit O, Agardh E, Agardh CD: Albuminuria and associated medical risk factors: a cross-sectional study in 451 type II (non-insulin-dependent) diabetic patients. Part 2. *J Diabetes Complications* 5:29–34, 1991
68. Østerby R, Gall M-A, Schmitz A, Nielsen FS, Nyberg G, Parving H-H: Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36:1064–1070, 1993
69. Nelson RG, Meyer TW, Myers BD, Bennett PH: Course of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *Kidney Int* 52 (Suppl. 63):S45–S48, 1997
70. Metcalf P, Baker J, Scott A, Wild C, Scragg R, Dryson E: Albuminuria in people at least 40 years old: effect of obesity, hypertension, and hyperlipidaemia. *Clin Chem* 38:1802–1808, 1992
71. Bigazzi R, Bianchi S, Campese VM, Baldari G: Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. *Nephron* 61:94–97, 1992
72. Rambausek M, Filser D, Ritz E: Albuminuria of hypertensive patients. *Clin Nephrol* 38 (Suppl. 1):S40–S45, 1992
73. U.K. Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: United Kingdom Prospective Diabetes Study 39. *BMJ* 317:713–720, 1998
74. Cowie CC, Port FK, Wolfe RA, Savage PA, Moll PA, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
75. Poulsen PL, Hansen KW, Mogensen CE: Ambulatory blood pressure in the transition from normo- to microalbuminuria: a longitudinal study in IDDM patients. *Diabetes* 43:1248–1253, 1996
76. U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998
77. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski AS: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
78. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
79. U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
80. Mogensen CE: Early glomerular hyperfiltration in insulin-dependent diabetes and late nephropathy. *Scand J Clin Lab Invest* 46:201–206, 1986
81. Chiarelli F, Verrotti A, Morgese E: Glomerular hyperfiltration increases the risk of developing microalbuminuria in diabetic children. *Pediatr Nephrol* 9:154–158, 1995
82. Caramori MLA, Pecis M, Gross JL, de Azevedo MJ: Glomerular filtration rate, urinary albumin excretion rate, and blood pressure changes in normoalbuminuric normotensive type 1 diabetic patients: an 8-year follow-up study. *Diabetes Care* 22:1512–1516, 1999
83. Yip JW, Jones SL, Wiseman MJ, Hill C, Viberti GC: Glomerular hyperfiltration in the prediction of nephropathy in IDDM: a 10-year follow-up study. *Diabetes* 45:1729–1733, 1996
84. Bognetti E, Meschi F, Bonfanti R, Gianolli L, Chiumello G: Decrease of glomerular hyperfiltration in short-term diabetic adolescents without microalbuminuria. *Diabetes Care* 16:120–124, 1993
85. Lervang H-H, Jensen S, Brochner-Mortensen J, Ditzel J: Early glomerular hyperfiltration and the development of late nephropathy in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 31:723–729, 1988
86. Allen TJ, Cooper ME, Gilbert RE, Winikoff J, Skinner SJ, Jerums G: Serum total renin is increased before microalbuminuria in diabetes. *Kidney Int* 50:902–907, 1996
87. Deinum J, Rønn B, Mathiesen E, Derkx FHM, Hop WCP, Schalekamp MADH: Increase in serum prorenin precedes onset of microalbuminuria in patients with insulin-dependent diabetes mellitus. *Diabetologia* 42:1006–1010, 1999
88. *Conquering Diabetes: A Report of the Congressionally-Established Diabetes Research Working Group 1999* (NIH publ. no. 99-4398) National Diabetes Information Clearinghouse, Bethesda, MD
89. American Diabetes Association: Diabetic nephropathy. *Diabetes Care* 23 (Suppl. 1):S69–S72, 2000
90. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D: 1998 Clinical practice guidelines for the management of diabetes in Canada: Canadian Diabetes Association. *Can Med Assoc J* 159 (Suppl. 8):S1–S29, 1998
91. Danne T, Kordonouri O, Hövener G, Weber B: Diabetic angiopathy in children. *Diabet Med* 14:1012–1025, 1997

Exhibit D

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Measurement of renal function in pre-ESRD patients

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Measurement of renal function in pre-ESRD patients. The measurement of renal function in pre-dialysis patients is important in order to determine the appropriate time to begin renal replacement therapy, to forecast the start, and to compare, in groups of patients, the efficiency of different treatments that limit renal disease progression. The most reliable methods, such as inulin clearance or measurement by radioisotopes, are too awkward for the usual clinical follow-up of patients. Although much simpler and almost as reliable, the use of iohexol radiologic contrast does not allow the frequent monitoring of the patient either. The determinations of the plasmatic creatinine and its clearance or the estimate of the glomerular filtration rate by means of equations derived from the creatinine are the methods most often used in order to measure renal function, although not without problems in pre-dialysis. In order to try to overcome such problems, more precise equations and procedures, including the measurement of averaged urea-creatinine clearance or creatinine clearance with cimetidine, have been designed that better estimate the glomerular filtration rate. However, none of these methods is totally reliable in pre-dialysis. A new endogen marker, cystatin C, has advantages over creatinine, though more studies are needed in pre-dialysis in order to ascertain its use. The initial proposal of the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (DOQI) guidelines to use weekly Kt/V and nutritional parameters to determine the time for starting renal replacement therapy has widened the prospects of the debate on the measurement of renal function in pre-dialysis, but further work is required to define their role in pre-dialysis patients' follow-up.

In pre-dialysis patients, the exact measurement of renal function is of crucial importance not just for determining the right time to start renal replacement therapy (RRT) but also in order to forecast its start and to compare, in large series of patients, the efficiency of the different treatments permitting reduced renal disease progression. An early start of dialysis, based exclusively on objective parameters, before the appearance of symptoms and signs of uremia, improves survival chances and reduces morbidity [1]. Apart from the classical parameters for determining the glomerular filtration rate (GFR), over the last few years, new determinations have been introduced such as the use of iohexol or cystatin C [2], as well as new concepts including the measurement of the Kt/V of urea or the evaluation of the nutritional state by means of the protein equivalent of total nitrogen appearance normalized to body weight (nPNA) in the study of pre-dialysis patients [3].

Each one of the tests available used in measuring the GFR, including the referenced technique (inulin clearance), has problems that are even greater in pre-dialysis patients. Therefore, the suitable determination of the renal function is still a subject of debate. Renal function as a whole does not mean, exclusively, GFR. Malnutrition related to uremia and its associated morbimortality must also be evaluated. Hence, the proposal of the DOQI guidelines is to use Kt/V and nutritional parameters as an indirect measurement of renal function and in order to determine when to start dialysis [3].

CLEARANCE BY ISOTOPES AND RADIOLOGIC CONTRASTS

The use of radioactive isotopes is a more practical method than that of inulin for calculating the GFR. Minimum differences are observed between the clearances (Cl) of these isotopes and that of inulin [4, 5]. From greater to lesser complexity, GFR can be calculated by measuring urinary Cl, plasmatic Cl, or from the images obtained with a gamma camera, the latter method being less precise in pre-dialysis patients [6].

Radioactive compounds give exact information on the GFR, but the majority of hospitals do not have access to them. The use of radiologic contrasts such as iohexol rather than radioactive markers has been proposed in order to calculate the renal Cl [7]. The plasmatic Cl of iohexol shows excellent correlation with plasmatic EDTA and inulin clearances [2, 8, 9]. It has also been shown to be very precise in the group of patients with moderate-severe renal insufficiency [10].

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Key words: Averaged creatinine-urea clearance, creatinine, creatinine clearance, cystatin C, Kt/V, nPNA, renal function.

Although the generalization of isotopic techniques, or with radiological contrasts, are advocated by some as the ideal method for measuring GFR [11], in clinical practice they are not so simple for quick and repetitive use with patients. Use seems more appropriate in clinical trials in which treatment for reducing renal disease progression is compared.

CREATININE

Plasmatic creatinine (Cr) concentration, because of its speed and simplicity, has been used as a usual measurement of GFR [12]. The main problems with interpreting Cr are chromogenes, extra-renal elimination, and a decrease in muscular mass. The substances called chromogenes influence the colorimetric reaction that measures plasmatic Cr, falsely increasing its value up to 20% [13]. In moderate to severe renal insufficiency, as plasmatic Cr is higher, the chromogenes contribute proportionally less (5%) [14].

In patients with severe chronic renal failure (CRF), it has been shown that an important part of Cr production is eliminated extra-renally; however, this occurs less often in patients with slight to moderate CRF. Estimated extra-renal creatinine clearance in advanced CRF is about 2 mL/min for a person weighing 70 kg. [15]. The extra-renal elimination mechanism of Cr in CRF is believed to be caused by degradation inside the intestinal light by bacterial flora [16].

The third problem in measuring Cr in CRF is the reduction in its production as the muscular mass decreases. When the GFR decreases to 25–50 mL/min, patients spontaneously reduce their protein intake [17], progressively leading to a decrease in the muscular mass, and, therefore, Cr generation [5]. So, plasmatic Cr is less than that expected for GFR.

Regarding the patient's nutritional status and renal function, plasmatic Cr has two facets. As an expression of renal function, the higher this is the more it is associated with the appearance of uremic symptoms. On the other hand, Cr reflects muscular mass. Patients with Cr under 10 mg/dL at the start of dialysis showed a greater mortality rate [18].

Because of the above problems, the measurement of plasmatic Cr does not precisely determine renal function in moderate to severe CRF.

CREATININE CLEARANCE

The measurement of creatinine clearance (C_{Cr}) resolves the problem of variability in the muscular mass, although it has other drawbacks: the collection of urine and the variation in the tubular secretion, which may overestimate or underestimate the GFR.

The incorrect collection of urine makes C_{Cr} calculation imprecise. Even in trained patients, the variation in Cr elimination because of urine collection problems is between 3% and 14%, reaching 70% in untrained patients [11, 19]. Greater C_{Cr} than plasmatic Cr variation from day to day indicates which is easier for detecting changes in the GFR with the Cr [12].

A substantial part of Cr excretion by the kidney is caused by tubular secretion. In patients with severe renal insufficiency, up to 60% of urinary Cr comes from tubular secretion [12, 20]. The relationship between fractional excretion of Cr and inulin is greatest between 20 and 25 mL/min/1.73 m^2, varying from 1.2 to 2.1, and it decreases in lower or greater values of Cl [20–23]. The bias introduced on measuring C_{Cr} with regard to that of iothalamate is approximately 5 mL/min/1.73 m^2 for a GFR of 25 mL/min/1.73 m^2 [23]. Also, there is marked variability in the magnitude of Cr secretion in each patient and in the same patient throughout the progression of the CRF [20], making it impossible to predict the changes in GFR from the changes in the C_{Cr} [24].

For all the above, the measurement of C_{Cr} is not useful in determining the exact level of renal function in predialysis. Some authors advocate that its routine use should be abandoned for evaluating CRF progression, given its great variability [11].

In order to compensate for the tubular secretion of Cr and the overestimation of GFR by the C_{Cr}, two solutions have been proposed: to calculate the Cl as the mean value between the urea and Cr clearances, and to calculate C_{Cr} after reducing the tubular secretion with cimetidine. Because the urea is reabsorbed and the urea clearance underestimates the GFR, it has been suggested that the mean of urea and Cr clearances may be used as the measurement of GFR in patients with CRF. This calculation does not have physiologic support and is subject to greater variability (four determinations), as well as the problems in collecting urine. Nevertheless, Lubowitz et al have shown that it can serve as a precise measurement of GFR in advanced CRF, correlating this with the clearance of inulin in patients with GFR < 20 mL/min/1.73 m^2 [25], and confirmed by other authors [5]. In patients with GFR < 15 mL/min/1.73 m^2 the measurement of the averaged clearances of urea and Cr more precisely estimates GFR [26].

In order to cancel the tubular secretion of Cr and thus avoid one of the sources of overestimating GFR in predialysis, oral administration of cimetidine, an organic cation like Cr that competitively reduces its secretion, has been proposed [27]. With cimetidine, the ratio between C_{Cr} and GFR approaches unity [20, 28, 29]. So far, only a limited number of patients have been studied using this method, and the dose and guidelines have not been determined.

Table 1. Equations

Cockroft-Gault	Cl creatinine (mL/min) = [140 − age (years)] × weight (kg)/ [72 × Cr (mg/dL)] multiply by 0.85 if female
MDRD7	GFR (mL/min/1.73 m^2) = 170 × Cr (mg/dL)$^{(-0.999)}$ × age$^{(-0.176)}$ × (0.762 if female) × (1.18 if black) × BUN (mg/dL)$^{(-0.170)}$ × Alb (g/dL)$^{(+0.318)}$
AASK	GFR (mL/min/1.73 m^2) = 222 × Cr (mg/dL)$^{(-0.675)}$ × age$^{(-0.203)}$ × (0.757 if female) × BUN (mg/dL)$^{(-0.548)}$ × Alb (g/dL)$^{(+0.572)}$
Nankivell	GFR (mL/min) = 6.7/Cr (mmol/L) + body weight (kg)/4 − urea (mmol/L)/2 − 100/height (m)^2 + 35 (male) or 25 (female)
Weekly Kt/V	Weekly Kt/V Daily urea clearance (L/day) × 7 / vol (L)
NPNA	(g/kg/day) = [6.49 × urine urea nitrogen (g/day) + 0.294 (g/L/day) × vol (L)]/[vol (L)]/0.58 (L/kg)]

ESTIMATION OF GFR BY FORMULAS DERIVED FROM PLASMATIC CREATININE

Different studies have shown the imprecision of C_{Cr} to measure GFR, being more precise using equations obtained from the plasmatic Cr [26, 30]. All developed equations consider the opposite of plasmatic Cr as the most important independent variable for calculating the GFR. [26]. The formulas include the weight, height, sex, age, race, and other variables multiplied by different correction factors [12]. These formulas are based on the idea that the excretion of Cr is constant and equal to its production, which, in turn, is proportional to muscular mass, and can be estimated from other variables [12]. In pre-dialysis patients with edemas, it is foreseeable that because of the increase in weight, GFR is overestimated with these formulas in a similar way to cirrhotic patients [31].

The simplest formula, and the most used, is that of Cockroft and Gault (Table 1). This equation was designed to calculate C_{Cr} in patients without renal disease [32]. Although showing a good correlation with the GFR calculated with isotopes (0.84), it overestimates the GFR in the low values and shows a great dispersion of the data and a high variability [30, 33, 34].

From the study "Modification of Diet in Renal Disease Study" (MDRD) several equations have been developed in order to predict GFR and have been verified in a large number of patients with diverse degrees of CRF. The most practical formula is number 7 (Table 1), which does not involve urine collection and includes demographic and seric factors like albumin, the Cr and the urea. Despite this, it was more precise for estimating the GFR than the C_{Cr} measured or estimated by Cockroft [26]. In the sub-group of patients with serum Cr greater than 2.5 mg/dL, precision was maintained for predicting the GFR. The equation has later been validated in pre-dialysis patients and in renal transplant patients [26].

In the group of African American patients included in the AASK study (African-American Study of Hypertension and Kidney Disease), the formula derived from the MDRD study predicted the GFR measured by I^{125}-lothalamate better than the C_{Cr} and the formula of Cockroft-Gault, although an even more precise formula was derived from this study for predicting GFR in black patients and with the same variables (Table 1) [35].

In renal transplant patients. Nankivell et al developed an equation (Table 1), which includes the value of plasmatic urea, with good correlation in all ranges of renal function compared with the GFR calculated with ^{99}Tc-DTPA, especially at low levels of GFR. This is being used in some transplant clinical trials, but its use has not become generalized, nor evaluated in other situations with CRF [36].

In general, in developing all these formulas, the more parameters taken into consideration, the greater the correlation with the GFR, which gives us an idea of the complexity of the work and of the multiple factors influencing GFR.

CYSTATIN C

Given the problems of plasmatic Cr, other endogen markers are being sought, the measurement of which in plasma will make it possible to know GFR. Although beta2-microglobulin increases progressively according to the decrease in renal function, its production is increased in certain pathologies, so generalized use in CRF has been ruled out [37].

Cystatin C could be the ideal marker. It is produced by the nucleated cells at a constant rate; it filters freely in the glomeruli and is reabsorbed only to be totally metabolised on a tubular level. Its production is unaffected by inflammatory or malign processes and is not muscular mass- or sex-dependent. Progressively simpler methods are being developed for its determination [2, 38, 39]. Plasmatic cystatin C correlates well and linearly with the GFR, so that it is more sensitive than Cr for detecting slight alterations in the GFR [40]. Cystatin C shows greater diagnostic precision than Cr (sensitivity 94%, specificity 95% vs. 94% and 80%) [41], although not confirmed in all studies and may not be generalized for all kinds of patients [42].

Additional studies are needed on patients with different degrees of renal function, in order to find out precisely the normal and pathologic levels of plasmatic cystatin C. Although having the obvious advantage of increasing in initial stages of renal insufficiency (which would lead, for example, to the indication of therapies or an earlier renal biopsy), it may not pose any benefit in pre-dialysis patient follow-up [43].

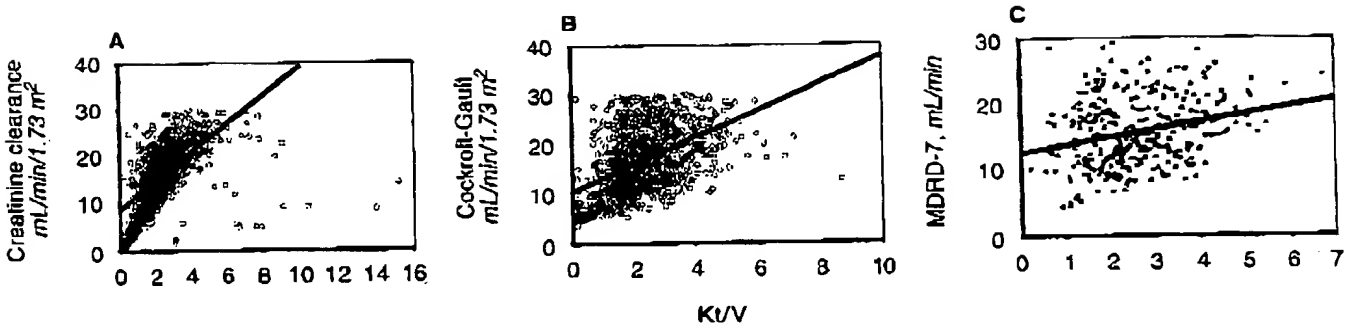

Fig. 1. Relationships of measured creatinine clearance (A), Cockroft-Gault equation (B), and MDRD-7 equation (C) to weekly Kt/V in pre-ESRD patients. Regression lines are represented by solid lines. $N = 1608$ measurements of creatinine clearance and Cockroft-Gault. $N = 321$ measurements of MDRD-7.

KT/V

From a practical point of view, we could choose another focus for measuring renal function and deciding on the start of substitute renal treatment. In 1995, Tattersall et al proposed the use of Kt/V, based on urea kinetic model and well-established as a useful method for determining the efficiency of dialysis, in order to decide the ideal time for starting RRT [44]. It is easy to determine in pre-dialysis patients: All that is needed is to know the daily urea elimination in order to calculate its clearance (K), the urea volume distribution (V), according to the Watson formulas [45], and apply the time (t) in which we wish to express it (daily or weekly) (Table 1).

The relationship between the seriousness of the clinical signs of uremia and the classical parameters of renal function like plasmatic Cr, urea, or C_{Cr} is low [46]. On the other hand, in the study by Tattersall, Kt/V correlated better than Cr or urea with the mortality, the hospitalization rate, and the number of days admitted; hence, the possible predictive role of the determination of Kt/V pre-dialysis [44].

In our out-patient population with clearances less than 30 mL/min/1.73 m^2 (1608 determinations in 214 women and 359 men, age range from 17 to 91 years), we have found that the measurement of weekly Kt/V correlates significantly with C_{Cr} ($r = 0.614$, $P < 0.000$), with those calculated with the Cockroft formula ($r = 0.477$, $P < 0.000$), and MDRD-7 (321 determinations, $r = 0.247$, $P < 0.000$) and, obviously by the mathematical relationship, with urea Cl ($r = 0.982$, $P < 0.000$) and mean urea-C_{Cr} ($r = 0.856$, $P < 0.000$) (Fig. 1). In the study by Kuhlmann et al, in 116 determinations Kt/V did not correlate with the Cockroft clearance and only slightly with C_{Cr} ($r = 0.183$, $P < 0.000$) [47]. Our findings are similar to those obtained by Mehrotra et al (Correlation Kt/V-C_{Cr}, $r = 0.78$, $P < 0.01$) [48]. Also, we found a significant inverse correlation between plasmatic Cr and Kt/V, both in the total of patients with clearances lower than 30 mL/min/1.73m^2 (1608 determinations, $r = -0.536$, $P < 0.000$), as well as in the sub-group with Kt/V less than 2.5 (968 determinations, $r = -0.52$, $P < 0.000$), unlike the results published earlier by Tattersall and Kuhlmann in a lesser number of patients [44, 47], though with the same dispersion of data. (Cr range for Kt/V less than 2.5 of 1 to 16.7 mg/dL, average 5.5 ± 2.4) (Fig. 2).

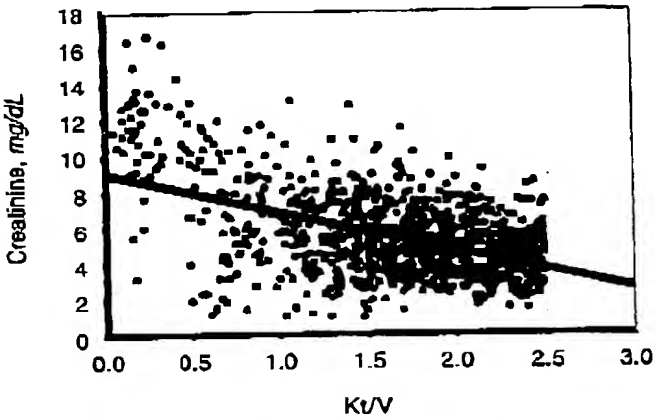

Fig. 2. Relationship of plasmatic creatinine to weekly Kt/V (weekly Kt/V < 2.5). Regression lines are represented by solid lines. $N = 968$ measurements.

As well as having a good correlation with the usual parameters for measuring renal function, does Kt/V correlate with nutritional parameters? In the studies by Mehrotra et al and by Jansen et al, no correlation was found between weekly Kt/V and plasmatic albumin, prealbumin, cholesterol, transferrin, body mass index, and in the subjective global assessment score (SGA). The only nutritional parameter with any correlation was nPNA, to which it is linked mathematically [48, 49]. In the study by Caravaca et al, the C_{Cr}, the averaged urea-C_{Cr}, and the Kt/V were compared in relation to a uremic score made up of uremic symptoms. SGA, serum albumin, and protein catabolism rate normalized for the ideal body weight in 201 patients checked in pre-dialysis consulta-

tion. The averaged Cl and that of the C_{Cr} correlated better with any degree of malnutrition and with the uremic score than with Kt/V [50]. In our group of patients with clearances lower than 30 mL/min/1.73 m² (354 determinations), we found that plasmatic albumin did not correlate with Kt/V ($r = 0.098$, $P = 0.065$) but did so with the C_{Cr} ($r = 0.138$, $P = 0.010$). averaged Cl ($r = 0.141$, $P = 0.008$), and Cockroft ($r = 0.228$, $P < 0.000$).

What would the appropriate Kt/V value be for starting RRT? The DOQI guidelines propose a weekly renal Kt/V of 2 as the threshold for starting dialysis [3]. It is assumed, therefore, that the risk of morbimortality in patients without dialysis with Kt/V less than 2 is similar to that of patients in continuous ambulatory peritoneal dialysis (CAPD) unsuitably treated [51]. However, this recommendation is based on indirect evidence and uncontrolled clinical data.

According to the NKF-DOQI guidelines for a weekly Kt/V of 2, an averaged urea-C_{Cr} of 10.5 mL/min/ 1.73 m² correlates [52]. We examined Kt/V sensitivity and specificity for detecting an averaged clearance less than 10.5 mL/min/1.73 m² in our group of determinations ($N = 1608$). There were 584 cases with averaged clearance less than or equal to 10.5 mL/min/1.73 m², of which 494 showed Kt/V less than or equal to 2. Of the 1024 with averaged clearance between 10.5 and 30 mL/min/1.73 m², there were 851 with Kt/V greater than 2. Sensitivity was 84.5%, specificity 83.1%, and the positive predictive value was 74.0%. Such moderate sensitivity and specificity conform with the correlation shown of Kt/V with the classical GFR determinations. Kuhlmann et al found a greater specificity (91.9%) and lower sensitivity (73.6%), but in a smaller number of tests [47].

However, Kt/V determination is also subject to errors, on the one hand those deriving from urine collection, and on the other, those related to the calculation of the urea volume distribution. Kt/V is greater in women than in men in different GFR ranges (averaged clearance <5 mL/min/1.73 m²: KT/V 1.31 + 0.25 vs. 1.09 + 0.19, $P = 0.001$; averaged clearance 5–10 mL/min/1.73 m²: Kt/V 2.22 + 0.41 vs. 1.83 + 0.38. $P < 0.0001$), which would suggest that it varies with V [50]. Patients with greater Kt/V generally have less urea distribution volume, independent of height, weight, age, and body surface area. Therefore, a patient with advanced CRF, undernourished and with low weight, could appear with higher Kt/V than that corresponding to him for his clearance, because of the decrease in V. On the other hand, an asymptomatic man, well-nourished with a clearance between 10 and 20 mL/min/1.73 m², could have a Kt/V < 2. [47].

Although the DOQI guidelines propose the use of Kt/V for monitoring the start of the RRT [3] do they provide anything more than the classic measurements of the GFR? Kt/V correlates well with GFR and has a moderate sensitivity and specificity for predicting the averaged clearance but does not correlate with the nutritional parameters, and its measurement can vary in relation to the V. Also, Kt/V has been related to the morbimortality after the start of RRT in a small group of patients. At present, the patients are starting RRT well below the ideal objective of Kt/V of 2 (UK 1.05, USA and Canada 0.7) [44, 51]. To assume the criteria of Kt/V 2 for the start of the RRT would mean beginning between 4 and 20 months before what is usual, with all this implies [53]. Larger and prospective studies are needed on the influence of Kt/V use when following up patients with advanced CRF before its use can be generalized.

NUTRITIONAL STATE

Over the past few years, the idea that the seriousness of the uremia should be evaluated by its deleterious effect on the nutritional state in pre-dialysis patients has gained support, centered on the relationship between protein intake and renal function [54]. The formulas that best predict GFR include nutritional parameters reflecting protein intake such as plasmatic albumin or urine urea elimination [26]. The risk of malnutrition increases as the renal function decreases, because of lower protein intake [17]. Patients with hypoalbuminemia at the start of dialysis were found to be at higher mortality risk [18]. Although the most important nutritional parameter in the studies is albumin, diverse factors influence this, thereby limiting its use as a nutritional marker [54].

nPNA (Table 1) has emerged as a useful and reproducible marker in patients with CRF [55]. Protein intake is an excellent marker of nutritional state, assuming the patient is not on a low-protein diet. Initial recommendations by the NKF-DOQI are to start dialysis when nPNA is less than 0.8 g/kg/day [3], although this recommendation does not appear in the revised version [52]. The nPNA value of 0.8 was derived from studies on patients in CAPD [56]. Mehrotra et al showed that in patients with continuous clearances (CAPD and pre-dialysis), a weekly Kt/V of 2 is required in order to maintain an nPNA of 0.9 g/kg/day [48], although this ratio may not be extended to other populations [49]. The recommendations in the DOQI guidelines cannot be directly applied to other countries without further studies.

In previous studies, nPNA measurement correlates with the GFR measured as averaged urea C_{Cr} ($r = 0.51$, $P < 0.0001$ and $r = 0.74$) [49, 50]. In our group of patients with clearance less than 30 mL/min/1.73 m² (1608 determinations), we found a correlation between nPNA and the averaged clearance ($r = 0.586$, $P < 0.000$) and the C_{Cr} ($r = 0.511$, $P < 0.000$) (Fig. 3) The use of nPNA under 0.8 g/kg/day to detect decreases in averaged Cl under 10.5 mL/min/1.73 m² shows low sensitivity (44.1%) but good specificity (87.7%).

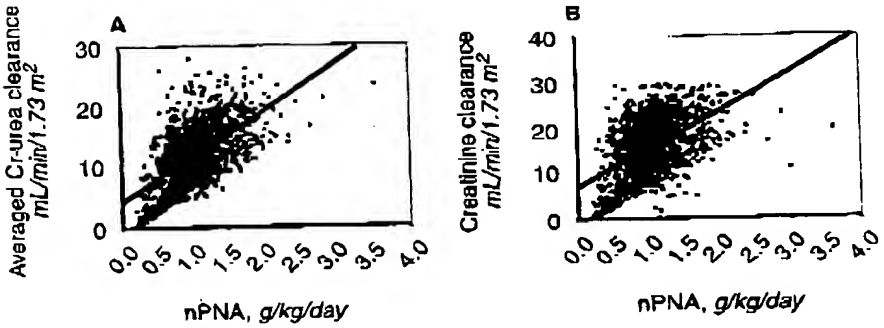

Fig. 3. Relationships of averaged creatinine-urea clearance (A), and creatinine clearance (B) to nPNA in pre-ESRD patients. Regression lines are represented by solid lines. N = 1608 measurements.

Larger, prospective, and well-controlled studies are needed in order to determine the use of nPNA measurement in the follow-ups of pre-dialysis patients and their correlation with mortality and morbidity after the start of the RRT.

CONCLUSION

The need to be able to measure renal function in pre-dialysis is obvious. In clinical trials carried out to determine which therapies reduce renal disease progression, it is important to know renal function exactly through the GFR. Currently, isotopic methods are the most reliable for determining GFR in pre-dialysis. The fact that they are not available at all centers means it is necessary to resort to the measurement of plasmatic Cr, Cr-derived equations, C_{Cr}, or the averaged urea C_{Cr}, training the patients for a careful collection of urine. In future, the generalization of techniques such as iohexol clearance or plasmatic cystatin will widen the possibilities of ascertaining pre-dialysis GFR correctly.

For the follow-up of each patient with advanced-terminal CRF, is it important to know the GFR precisely? In most clinical situations an exact knowledge of GFR is not required, it being enough to know whether GFR is getting better or worse, which can be evaluated using plasmatic Cr. An intermediate solution is to determine GFR periodically by means of averaged urea-Cr clearance or the equations based on Cr (Cockroft, MDRD-7, Nankivell) and carry out the usual patient follow-up with plasmatic Cr determination.

The usual clinical practice until now for including a patient in RRT, before the appearance of uremic symptoms, was based on estimating GFR from the urea and the plasmatic Cr, but there is no linear relationship between renal function as GFR and uremia [50]. Although more and larger studies are needed in order to find out its global contribution, it seems appropriate to add Kt/V and the evaluation of the nutritional state using nPNA or SGA as an indirect measurement of pre-dialysis renal function in order to reduce the morbimortality of patients.

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REFERENCES

1. Bonomini V, Feletti C, Scolari MP, Stefoni S: Benefits of early initiation of dialysis. *Kidney Int* 28(Suppl 17):S57–S59, 1985
2. Nilsson-Ehle P, Grubb A: New markers for the determination of GFR: Iohexol clearance and cystatin C concentration. *Kidney Int* 46(Suppl. 47):S17–S19, 1994
3. National Kidney Foundation-Dialysis Outcomes Quality Initiative: Initiation of dialysis. *Am J Kidney Dis* 30(Suppl 2): S70–S73, 1997
4. Perrone RD, Steinman TI, Beck GJ, *et al*: Utility of radioisotopic filtration markers in chronic renal insufficiency: Simultaneous comparison of ^{125}I-iothalamate, ^{169}Yb-DTPA, ^{99m}Tc-DTPA, and inulin. *Am J Kidney Dis* 16:224–235, 1990
5. Levey AS: Measurement of renal function in chronic renal disease. *Kidney Int* 38:167–184, 1990
6. De Santo NG, Anastasio P, Cirillo M, *et al*: Measurement of glomerular filtration rate by the ^{99m}Tc-DTPA renogram is less precise than measured and predicted creatinine clearance. *Nephron* 81:136–140, 1999
7. Dalmeida W, Suki WN: Measurement of GFR with non-radioisotopic radio contrast agents. *Kidney Int* 43:725–728, 1988
8. O'Reilly PH, Brooman PJC, Martin PJ, *et al*: Accuracy and reproducibility of a new contrast clearance method for the determination of glomerular filtration rate. *BMJ* 293:234–236, 1986
9. Brandstrom E, Grzegorczyk A, Jacobsson L, *et al*: GFR measurements with iohexol and ^{51}Cr-EDTA: A comparison of the two favoured GFR markers in Europe. *Nephrol Dial Transplant* 38:1176–1182, 1998
10. Gaspari F, Perico N, Matalone M, *et al*: Precision of plasma clearance of iohexol for estimation of GFR in patients with renal disease. *J Am Soc Nephrol* 9:310–313, 1998
11. Walser M: Assessing renal function from creatinine measurements in adults with chronic renal failure. *Am J Kidney Dis* 32:23–31, 1998
12. Perrone RD, Madias NE, Levey AS: Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 38:1933–1953, 1992
13. Molitch ME, Rodman E, Hirsch CA, Dubinsky E: Spurious serum creatinine elevations in ketoacidosis. *Ann Intern Med* 93:280–281, 1980
14. Doolan PD, Alpen EL, Theil GB: A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. *Am J Med* 32:65–79, 1962
15. Mitch WE, Collier VU, Walser M: Creatinine metabolism in chronic renal failure. *Clin Sci* 58:327–335, 1980
16. Dunn SR, Gabuzda GM, Superdock KR, *et al*: Induction of creat-

ininase activity in chronic renal failure: Timing of creatinine degradation and effect of antibiotics. *Am J Kidney Dis* 28:72–77, 1997
17. IKIZLER TA, GREENE JH, WINGARD RL, *et al*: Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 6:1386–1391, 1995
18. UNITED STATES RENAL DATA SYSTEMS: USRDS 1992: Comorbid conditions and correlations with mortality risk among 5399 incident hemodialysis patients. *Am J Kidney Dis* 20(Suppl 2):S32–S38, 1992
19. SINTON TC, DE LEACY EA, COWLEY DM: Comparison of ^{51}Cr EDTA clearance with formulae in the measurement of glomerular filtration rate. *Pathol* 18:445–447, 1986
20. SHEMESH O, GOLBETZ H, KRISS JP, MYERS BD: Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28:830–838, 1985
21. GIOVANETTI S, BARSOTTI G: In defense of creatinine clearance. *Nephron* 59:11–14, 1991
22. BAUER JH, BROKS CS, BURCH RN: Renal function studies in man with advanced renal insufficiency. *Am J Kidney Dis* 2:30–35, 1982
23. CORESH J, TOTO RD, KIRK KA, and the AASK pilot study investigators: Creatinine clearance as a measure of GFR in screens for the African-American study of Kidney disease and hypertension pilot study. *Am J Kidney Dis* 32:32–42, 1998
24. WALSER M, DREW HH, LAFRANCE ND: Creatinine measurements often yield false estimates of progression in chronic renal failure. *Kidney Int* 34:412–418, 1988
25. LEIBOWITZ H, SLATOPOLSKY E, SHANKEL S, *et al*: Glomerular filtration rate: Determination in patients with chronic renal disease. *JAMA* 199:100–104, 1969
26. LEVEY AS, BOSCH JP, LEWIS JB, *et al*: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med* 130:877–884, 1999
27. OLSEN NV, LADEFOGED SD, FELDT-RASMUSSEN B, *et al*: The effects of cimetidine on creatinine excretion, glomerular filtration rate and tubular function in renal transplant recipients. *Scand J Clin Lab Invest* 49:155–159, 1989
28. VAN ACKER BAC, KOOMEN GCM, KOOPMAN MG, *et al*: Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 340:1326–1329, 1992
29. HILDRANDS L, ARTZ MA, WETZELS JF, KOENE RA: Cimetidine improves the reliability of creatinine as a marker of glomerular filtration. *Kidney Int* 40:1171–1176, 1991
30. TOTO RD, KIRK KA, CORESH J, and the AASK pilot study investigators: Evaluation of serum creatinine for estimating glomerular filtration rate in African Americans with hypertensive nephrosclerosis: Results from the African-American Study of Kidney Disease and Hypertension (AASK). *J Am Soc Nephrol* 8:279–287, 1997
31. COCCHETTO DM, TSCHANZ C, BJORNSSON TD: Decreased rate of creatinine production in patients with hepatic disease: Implications for estimation of creatinine clearance. *Ther Drug Monit* 5:161–168, 1983
32. COCKROFT D, GAULT MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
33. GAULT MH, LONGERICH LL, HARNETT JD, WESOLOWSKI C: Predicting glomerular function from adjusted serum creatinine. *Nephron* 62:249–256, 1992
34. WALSER M, DREW HH, GULDAN JL: Prediction of glomerular filtration rate from serum creatinine concentration in advanced chronic renal failure. *Kidney Int* 44:1145–1148, 1993
35. LEWIS J, AGODOA L, CHEEK D, *et al* for the African-American Study of hypertension and kidney disease: Comparison of cross-sectional function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. *Am J Kidney Dis* 38:744–753, 2001
36. NANKIVELL BJ, GRUENEWALD SM, ALLEN RDM, CHAPMAN JR: Predicting glomerular filtration rate after kidney transplantation. *Transplantation* 59:1683–1689, 1995
37. KARLSSON FA, WIDELL L, EVRIN PE: Beta2-Microglobulin in clinical medicine. *Scand J Clin Lab Invest* 40(Suppl 154):S27–S37, 1980
38. NEWMAN DJ, THAKKAR H, EDWARDS RG, *et al*: Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 47:312–318, 1995
39. RANDERS E, KRISTENSEN JH, ERLANDSEN EJ, DANIELSEN H: Serum cystatin C as a marker of the renal function. *Scand J Clin Lab Invest* 58:585–592, 1998
40. COLL E, BOTEY A, ALVAREZ L, *et al*: Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis* 36:205–207, 2000
41. MEJER P, FROIDEVAUX C, DAYER E, BLANC E: Cystatin C concentration and glomerular filtration rate. *Lancet* 357:634–635, 2001
42. ODDOZE C, MORANGE S, PORTUGAL H, *et al*: Cystatin C is not more sensitive than creatinine for detecting early renal impairment in patients with diabetes. *Am J Kidney Dis* 38:310–316, 2001
43. DEINUM J, DERKX FHM: Cystatin for estimation of glomerular filtration rate? *Lancet* 356:1624–1625, 2000
44. TATTERSALL J, GREENWOOD R, FARRINGTON K: Urea kinetics and when to commence dialysis. *Am J Nephrol* 15:283–289, 1995
45. WATSON PE, WATSON ID, BATT RD: Total body water volumes for adult males and females estimated from anthropomorphic measurements. *Am J Clin Nutr* 33:27–39, 1980
46. MALANGONE JM, ABUELO JG, PEZZULLO JC, *et al*: Clinical and laboratory features of patients with chronic renal disease at the start of dialysis. *Clin Nephrol* 31:77–87, 1989
47. KUHLMANN MK, HECKMANN M, RIEGEL W, KÖHLER H: Evaluation of renal Kt/V as a marker of renal function in predialysis patients. *Kidney Int* 60:1540–1546, 2001
48. MEHROTRA R, SARAN R, MOORE HL, *et al*: Toward targets for initiation of chronic dialysis. *Perit Dial Int* 17:497–508, 1997
49. JANSEN MA, KOREVAAR JC, DEKKER FW, NECOSAD STUDY GROUP: Renal function and nutritional status at the start of chronic dialysis treatment. *J Am Soc Nephrol* 12:157–163, 2001
50. CARAVACA F, ARROBAS M, PIZARRO JL, SÁNCHEZ-CASADO E: Uraemic symptoms, nutritional status and renal function in pre-dialysis end-stage renal failure patients. *Nephrol Dial Transplant* 16:776–782, 2001
51. CHURCHILL DN, TAYLOR DW, KESHAVIAH PR, CANADA-USA (CANUSA) PERITONEAL DIALYSIS STUDY GROUP: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J Am Soc Nephrol* 7:198–207, 1996
52. NKF-DOQI: Clinical practice guidelines for peritoneal dialysis adequacy: Update 2000. *Am J Kidney Dis* 37:(Suppl)S68–S71, 2001
53. BURKART JM: Clinical experience: How much earlier should patients really start renal replacement therapy? *J Am Soc Nephrol* 9:(Suppl):118–S123, 1998
54. HAKIM RM, LAZARUS JM: Initiation of dialysis. *J Am Soc Nephrol* 6:1319–1328, 1995
55. POLLOCK CA, IBELS LS, ALLEN BJ: Nutritional markers and survival in maintenance dialysis patients. *Nephron* 74:625–641, 1996
56. BLUMENKRANTZ MJ, KOPPLE JD, MORAN JK, COBURN JW: Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. *Kidney Int* 21:849–861, 1982

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DORLAND'S ILLUSTRATED

Medical Dictionary

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a predisposition to arteriosclerosis and in those who have hypertension resulting from an apparent underlying disease, such as pheochromocytoma. Called also *hyaline arteriolar n.* **hyaline arteriolar n.,** benign n. **hyperplastic arteriolar n.,** malignant n. **intercapillary n.,** arteriolar n. **malignant n.,** an uncommon form of arteriolar nephrosclerosis affecting all the vessels of the body, especially the small arteries and arterioles of the kidneys, and frequently associated with malignant hypertension and hyperplastic arteriolosclerosis. It may occur in the absence of previous history of hypertension, or may be superimposed on benign hypertension or primary renal disease, especially glomerulonephritis, benign nephrosclerosis, and pyelonephritis. Called also *hyperplastic arteriolar n.* and *Fahr-Volhard disease.* **senile n.,** nephrosclerosis which is just a part of the arteriosclerosis common in old age.

nephroscope (nef′ro-skōp) an instrument inserted into an incision in the renal pelvis for viewing the inside of the kidney, equipped with three channels for telescope, fiberoptic light input, and irrigation.

nephroscopy (nĕ-fros′ko-pe) visualization of the kidney by means of the nephroscope.

nephroses (nĕ-fro′sēz) plural of *nephrosis.*

nephrosis (nĕ-fro′sis), pl. *nephro′ses* [*nephr-* + *-osis*] any disease of the kidney, especially any disease of the kidneys characterized by purely degenerative lesions of the renal tubules—as opposed to nephritis—and marked by edema (noninflammatory), albuminuria, and decreased serum albumin (the nephrotic syndrome). **acute n.,** nephrosis marked by scanty urine but with little edema or albuminuria. **amyloid n.,** chronic nephrosis with amyloid degeneration of the median coat of the arteries and the glomerular capillaries; amyloid kidney. **avian n.,** infectious bursal disease. **cholemic n.,** renal disease associated with various types of hepatic or biliary dysfunction, especially those in which there is obstructive jaundice. **chronic n.,** renal disease characterized by chronic degeneration of the renal epithelium. **Epstein's n.,** a type of chronic tubular nephritis resulting from systemic metabolic disorder, occurring usually in young persons and in women, and frequently associated with hypothyroidism or other endocrine disturbance. **glycogen n.,** nephrosis associated with glycogen vacuolation within the proximal convoluted tubules and the loops of Henle. **hydropic n.,** vacuolar n. **hypokalemic n.,** vacuolar n. **infectious avian n.,** infectious bursal disease. **larval n.,** a condition in which the renal lesions are slight and manifested clinically by albuminuria. **lipid n., lipoid n.,** nephrosis characterized by edema, albuminuria, and changes in the protein and lipids of the blood and the accumulation of globules of cholesterol esters in the tubular epithelium of the kidney. **lower nephron n.,** a condition of renal insufficiency leading to uremia, due to necrosis of the cells of the lower nephron, blocking the tubular lumens of this region. The condition is seen after severe injuries, especially crushing injury to muscles (*crush syndrome*). **necrotizing n.,** renal disease characterized by necrosis of tubular epithelium of the kidney. **osmotic n.,** vacuolar n. **toxic n.,** nephrosis caused by some toxic agent, most frequently and typically by bichloride of mercury. **vacuolar n.,** renal disease in which injury of the renal tubules is associated with vacuolization of the proximal convoluted tubules and sometimes of the loops of Henle and collecting tubules, presumed to be caused by disturbances in the normal osmotic relationships within the cells. These changes are seen in various clinical situations, as following the administration of hypertonic solutions, in diseases resulting in marked alterations in fluid balance, and in severe hypokalemia. Called also *hydropic n., hypokalemic n.,* and *osmotic n.*

nephrosonephritis (nĕ-fro″so-nĕ-fri′tis) [*nephrosis* + *nephritis*] renal disease with nephrotic and nephritic components. **hemorrhagic n., Korean hemorrhagic n.,** epidemic hemorrhagic fever.

nephrosonography (nef″ro-so-nog′rah-fe) ultrasonic scanning of the kidney.

nephrospasis (nef″ro-spas′is) [*nephro-* + Gr. *span* to draw] movable kidney in which the natural supports of the organ are so weakened that the organ hangs by its pedicle.

nephrostolithotomy (nĕ″fro-sto-lĭ-thot′o-me) [*nephro-* + Gr. *lithos* stone + Gr. *tomē* a cutting] removal of renal calculi through a nephrostomy tube inserted through the abdominal wall into the renal pelvis.

nephrostoma (nĕ-fros′to-mah) [*nephro-* + Gr. *stoma* mouth] one of the funnel-shaped and ciliated orifices of excretory tubules that open into the coelom in the embryo, best seen in lower vertebrates.

nephrostome (nef′ro-stōm) nephrostoma.

nephrostomy (nĕ-fros′to-me) [*nephro-* + Gr. *stomoun* to provide with an opening, or mouth] the creation of a fistula leading directly into the pelvis of the kidney.

nephrotic (nĕ-frot′ik) pertaining to, resembling, or caused by nephrosis.

nephrotome (nef′ro-tōm) one of the segmented divisions of the mesoderm connecting the somite with the lateral plates of unsegmented mesoderm; it is the source of much of the urogenital system. Called also *intermediate cell mass* and *middle plate.*

nephrotomogram (nef″ro-to′mo-gram) the sectional radiograph of the kidney obtained by nephrotomography.

nephrotomography (nef″ro-to-mog′rah-fe) radiologic visualization of the kidney by tomography after intravenous introduction of contrast medium as a bolus or by infusion.

nephrotomy (nĕ-frot′o-me) [*nephro-* + Gr. *tomē* a cutting] a surgical incision into the kidney. **abdominal n.,** nephrotomy performed through an incision into the abdomen. **anatrophic n.,** incision into the kidney between its vascular segments, to minimize bleeding and parenchymal injury and to prevent atrophy. **lumbar n.,** nephrotomy performed through an incision into the loin.

nephrotoxic (nef″ro-tok′sik) toxic or destructive to kidney cells.

nephrotoxicity (nef″ro-tok-sis′ĭ-te) the quality of being toxic or destructive to kidney cells.

nephrotoxin (nef″ro-tok′sin) [*nephro-* + Gr. *toxikon* poison] a toxin which has a specific destructive effect on kidney cells.

nephrotropic (nef″ro-trop′ik) having a special affinity for or exerting its principal effect upon kidney tissue.

nephrotuberculosis (nef″to-tu-ber″ku-lo′sis) [*nephro-* + *tuberculosis*] disease of the kidney due to *Mycobacterium tuberculosis.*

nephroureterectomy (nef″ro-u″re-ter-ek′to-me) [*nephro-* + *ureterectomy*] excision of a kidney and a whole or part of the ureter.

nephroureterocystectomy (nef″ro-u-re″ter-o-sis-tek′to-me) [*nephro-* + Gr. *ourētēr* ureter + *kystis* bladder + *ektomē* excision] excision of the kidney, ureter, and a portion of the bladder wall.

nephrozymosis (nef″ro-zi-mo′sis) zymotic or fermentative disease of the kidney.

nephrydrosis (nef″rĭ-dro′sis) [*nephro-* + Gr. *hydōr* water + *-osis*] hydronephrosis.

nephrydrotic (nef″rĭ-drot′ik) pertaining to nephrydrosis.

nepiology (nep″e-ol′o-je) [Gr. *nēpio* infant + *-logy*] (*obs.*) the department of pediatrics treating of young infants.

Neptazane (nep′tah-zān) trademark for a preparation of methazolamine.

neptunium (nep-tu′ne-um) [from planet Neptune] a radioactive element of atomic number 93 and atomic weight 237, occurring in certain earths and obtained by splitting the uranium atom with neutrons. It is unstable and changes into plutonium. Symbol Np.

nequinate (nĕ-kwin′āt) chemical name: 6-butyl-1,4-dihydro-4-oxo-7-(phenylmethoxy)-3-quinolinecarboxylic acid methyl ester; a coccidiostat for poultry, $C_{22}H_{23}NO_4$.

Nerium (ne′rĭ-um) a genus of evergreen apocynaceous shrubs of the Mediterranean region and Asia. *N. odorum* (*N. indicum*) is the sweet-scented oleander; *N. oleander* L. is the common oleander.

Nernst equation, potential (nernst) [Walther Hermann *Nernst,* German physical chemist, 1864–1941] see under *equation* and *potential.*

nerol (ne′rol) an essential oil, $(CH_3)_2C{:}CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3){:}CH \cdot CH_2OH$, a constituent of orange flower oil.

neroli (ner′o-le) an essential oil distilled from orange blossoms; orange flower oil.

nerval (ner′val) (*obs.*) neural.

nerve (nerv) [L. *nervus;* Gr. *neuron*] a cordlike structure,